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RECURRENT ACUTE PANCREATITIS: OBSERVATIONS ON ETIOLOGY AND SURGICAL TREATMENT *†

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THE WIDE USE OF SIMPLE LABORATORY PROCEDURES for the determination of serum amylase has revealed several facts regarding pancreatitis.

1. It is a common disease and varies in intensity from mild attacks to a fulminating catastrophe. Fortunately the latter event is a small proportion of the total cases.

2. Recurrence is common and may be anticipated. With repeated attacks there may be progressive destruction of functioning pancreatic tissue with pathologic changes in the gland and deficiencies in external and internal secretions.[1] On the other hand, in some patients after many years of recurrent attacks no measurable or visible changes occur in the gland.

3. Pancreatitis is frequently associated with biliary tract disease. Many disorders heretofore termed post-cholecystectomy syndrome, biliary dyskinesia etc. are actually recurrent attacks of pancreatitis.[2]

Previous factual knowledge has been available for many years, since Opie[3] in 901 described the reflux mechanism. This is dependent on an anatomic variation in the entrance of the main pancreatic duct to the duodenum which creates a common biliary-pancreatic passageway, thus permitting bile to flow into the pancreas. The immediate bile diverting mechanism in Opie's case was a stone lodged in the ampulla of Vater. Archibald,[4] in 1919, showed that a similar bile diverting mechanism could be brought about by spasm of the sphincter of Oddi.

The effectiveness of surgical management of the disease has not kept pace with the knowledge of what must be the mode of production in at least

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a large number of cases. Decompression of the biliary tract by drainage to prevent reflux is effective only so long as the drain remains. Sympathectomy to interrupt pain sensation is not a direct attack on the disease. Section of the esophageal vagus to paralyze the sphincter of Oddi might be effective but it deprives the gastro-intestinal tract of that innervation. Local nerve interruption[5] seems rational but is technically difficult and its effect is temporary,

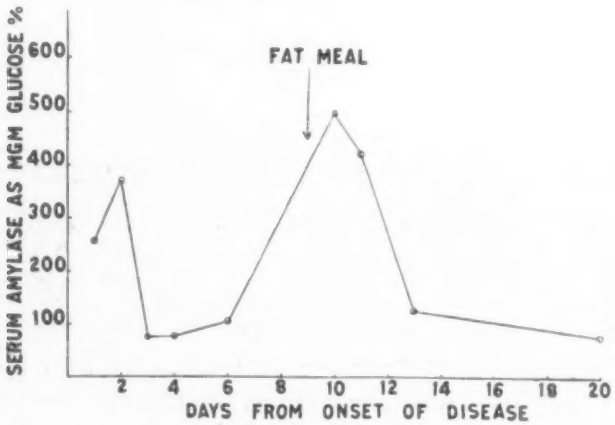

FIG. 1. — (Case 13) Serum amylase determinations demonstrate recovery from an attack of acute pancreatitis and recurrence following administration of a fat meal.

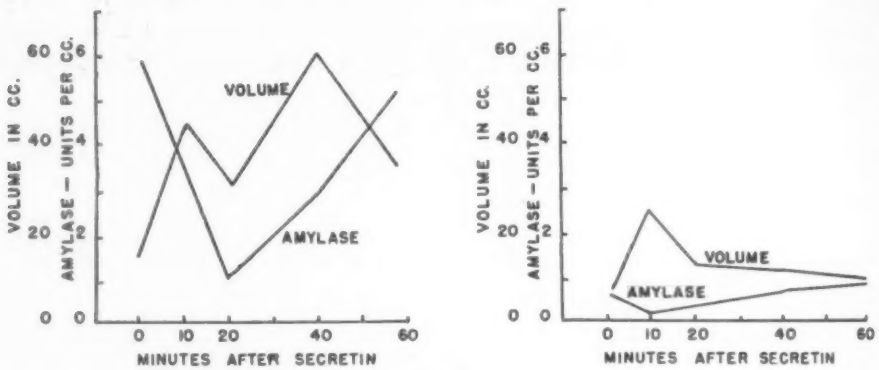

FIG. 2.—Quantitative evaluations of pancreatic functions.

apparently due to regeneration of the nerves.[6] Archibald first directly approached the problem by cutting the sphincter of Oddi in a human patient with recurrent pancreatitis.[7] He had noted the uniformly good results which followed removal of a stone impacted in the ampulla, when, perforce, the sphincter had to be cut.

Studies on patients with proven recurrent pancreatitis substantiate Archibald's contention that when a common passageway exists spasm of the

sphincter will produce the disease and sectioning of the sphincter will relieve the disease. The study here reported was conducted on the basis of the following concepts:

A. That serum amylase determinations during an attack will establish the diagnosis of acute pancreatitis (Fig. 1). In the absence of a rise in serum amylase the diagnosis is not necessarily excluded. With long standing disease and fibrosis or calcification of the gland there may be no rise in serum amylase or the level may be low.

B. That the intravenous administration of an assayed quantity of secretin will produce a flow of pancreatic juice which, when collected through a

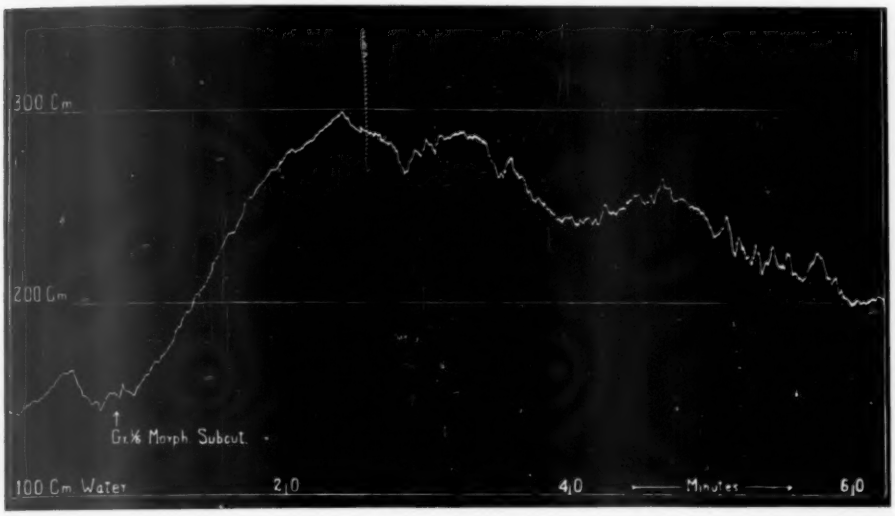

FIG. 3.—Effect of morphine on the sphincter of Oddi. Kymographic tracing of the resistance of the human sphincter of Oddi as measured through a T tube in the common duct, shows that the normal resistance of the sphincter (150 mm. of water) rises to 300 mm. and gradually subsides to 200 mm. in 1 hour. The effect persists for 4 hours.

duodenal tube, can be measured for total amount, amylase content, and bicarbonate content. The measurements are quantitative evaluations of pancreatic functions (Fig. 2).

C. That the administration of morphine will produce spasm of the duodenal wall and resistance to pancreatic and biliary flow, as demonstrated by kymographic pressure tracings recorded through a T tube in the common bile duct (Fig. 3). Ccholangiograms done through a T tube in the common bile duct also demonstrate the contraction of the duodenal wall and resistance to the flow of bile (Fig. 4 & 5).

D. The N/10 Hydrochloric acid applied to the papilla of Vater will produce spasm of the sphincter of Oddi, as demonstrated by kymographic pressure tracings taken through a T tube in the common bile duct (Fig. 6), and in cholangiograms done through a T tube (Fig. 7). This same spasm can be

FIG. 4.

FIG. 5.

FIGS. 4 and 5.—A cholangiogram through a T tube 2 weeks after transduodenal sphincterotomy for ampullary stone, shows ready entrance of contrast medium into the duodenum (Fig. 4). Following administration of morphine (Fig. 5) the compression of the intramural portion of the common bile duct by the increased tonus of the duodenal wall is demonstrated.

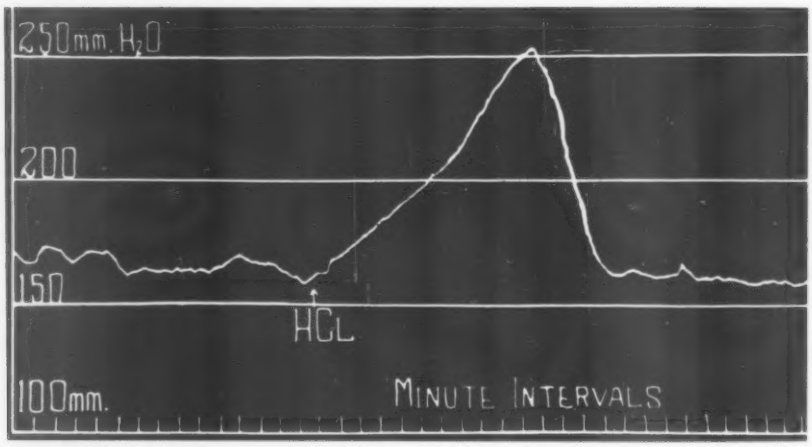

FIG. 6.—Kymographic tracing of the resistance of the sphincter as measured through a T tube in the common duct. The resistance of flow rises from 150 to 250 mm. of water. The effect lasts about 10 minutes.

produced by sudden, painful distension of the common duct through a T tube (Fig. 8 & 9).

E. That operative cholangiograms done by injecting contrast medium through a needle into the cystic or common duct at the same time that N/10

FIG. 7.—Cholangiogram performed through a cystic duct tube 2 weeks after cholecystectomy (sphincter intact). Hydrochloric acid applied directly to the papilla through a duodenal tube causes spasm and reflux of contrast medium into the pancreatic duct (arrow).

hydrochloric acid is applied to the papilla can demonstrate the passageway (Fig. 10).

F. That, after section of the sphincter muscle, the hydrochloric acid effect on the papilla is abolished (Fig. 11). The sphincter can no longer become spastic and biliary reflux under pressure is prevented. The morphine effect on the duodenal wall persists. Thus, reflux of the duodenal contents into the

biliary tract is prevented. In one patient with calcified pancreas and distortion of the duodenum and papilla, the muscle was incompletely sectioned as shown by kymographic tracings after hydrochloric acid application to the papilla (Fig. 12 & 13). This patient's pain was relieved, however, presumably because the resistance created by the remaining muscle fibers was insufficient to force bile into the pancreatic duct.

In patients whose pancreatic fibrosis is marked and pancreatic function diminished, sectioning of the sphincter relieves pain but does not restore normal digestion until the pancreas has regenerated which may take several weeks to months. (Fig. 14).

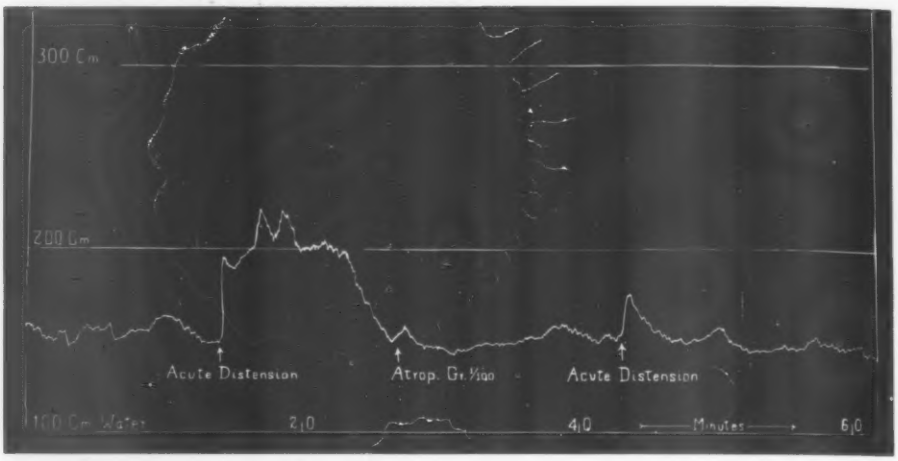

FIG. 8.—Effect of sudden distention of the common bile duct in the human through a cystic duct tube. Reflex spasm of the sphincter of Oddi raises the resistance to flow from 150 mm. to 225 mm. of water. The effect lasts about 10 minutes. Previous atropinization reduces this reflex spasm.

The actual sectioning of the sphincter is a somewhat exacting procedure. The papilla is difficult to find and when the muscle is in spasm the orifice may be extremely small. The best approach is through the common bile duct. An instrument* described by Colp and Doubilet[9] for performing this operation without opening the duodenum has been used successfully in those patients whose sphincters are not in marked spasm or in whom there is no marked distortion or narrowing of the common duct. The duodenum may be opened over an instrument or over a probe. The muscle is then cut over the probe for about 1 cm. in the anterior free or intraluminary portion of the duct. The retraction of the sphincter muscle fibers prevents heating or regeneration of the muscle.

CASE SUMMARIES

Case No. 1—M.H. (Bellevue Hospital, No. 10199-47) was a 51-year-old female with a 22-year-old history of attacks of severe epigastric pain, lasting from 1 to 7 days, and increasing in frequency until they occurred every two weeks. In addition, there

* Manufactured by The American Cystoscope Makers, New York, N. Y.

was almost daily transient epigastric pain after meals. Cholecystectomy was performed 20 years ago, and a choledochostomy and duodenostomy 7 years ago for an attack accompanied by jaundice. At that operation the jaundice was found to be due to a pancreatitis. She was admitted to Bellevue Hospital on February 24, 1947 during an attack of severe epigastric and left upper quadrant pain, associated with fever and paralytic ileus. At no time was the serum amylase elevated. The secretin test showed

FIG. 9.—Cholangiogram performed through a T tube in the common duct. Sudden distention of the common duct by contrast medium causes pain and reflex spasm of the sphincter of Oddi. In this patient, due to a common passage, the contrast medium was forced up the main pancreatic duct (black arrow) and into the accessory pancreatic duct (white arrow) which can be seen to empty into the duodenum proximal to the papilla of Vater.

diminished function (total volume 104 cc; amylase 125 units). X-ray examination of the stomach and duodenum was reported normal.

At operation on March 24, 1947 the pancreas was uniformly enlarged and indurated. The common bile duct was moderately dilated. A cholangiogram showed pancreatic reflux when spasm of the sphincter of Oddi was induced by acid. Endo-

FIG. 10.—(Case 16) Operative cholangiogram in a patient with recurrent acute pancreatitis. Contrast medium injected through a needle in the cystic duct at the same time as hydrochloric acid was applied to the papilla of Vater through a duodenal tube, was forced into the pancreatic duct, visualizing it throughout its length. (arrow).

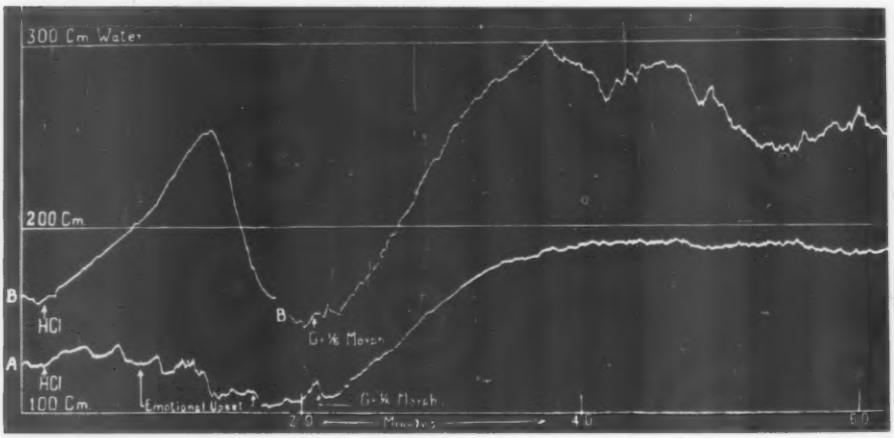

FIG. 11.—(Case 1) Kymographic tracing (A) recorded through a T tube in the common duct of the resistance to flow of bile into the duodenum in Case No. 1, indicates that the sphincter of Oddi is destroyed functionally since there is no response either to local application of acid or to emotional stimuli. The response to morphine is limited to its action on duodenal musculature. This tracing can be compared to the response of the intact sphincter to acid and morphine (B, superimposed).

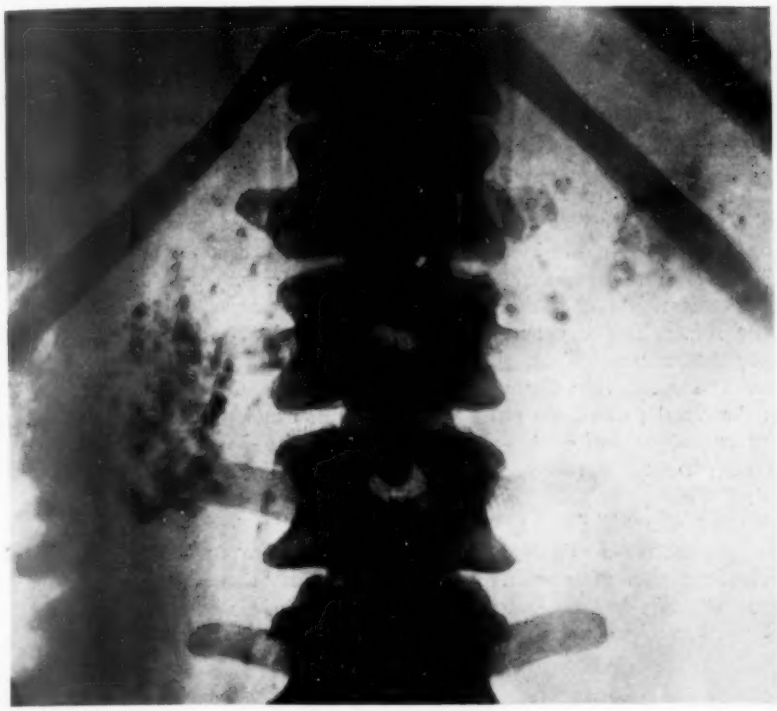

FIG. 12.—(Case 15). Calcification of the pancreas.

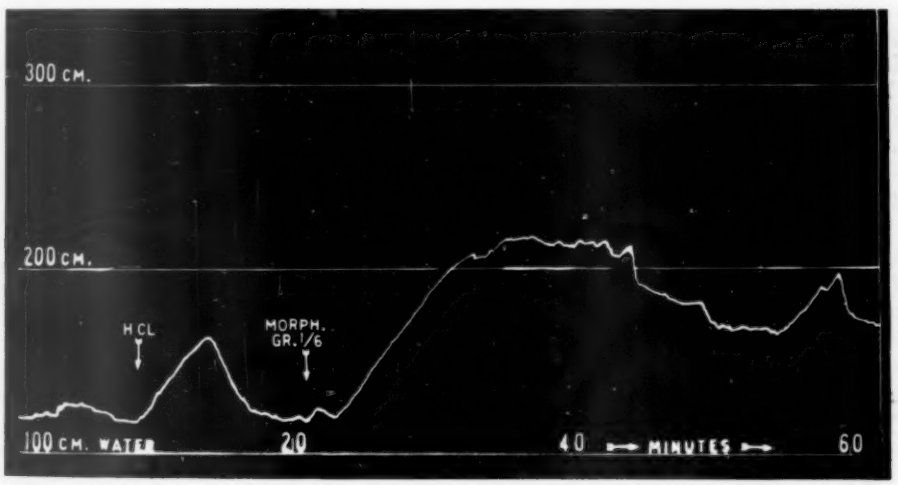

FIG. 13.—(Case 15). Kymographic tracing, recorded through a T tube in the common duct, of the resistance to flow of bile into the duodenum 2 weeks after sphincterotomy, reveals incomplete section of the sphincter of Oddi, since there is a mild response to hydrochloric acid. The response to morphine however, shows adequate destruction of the sphincter muscle.

choledochal sphincterotomy was performed and the common duct drained by a T tube. Two weeks after operation, cholangiographic studies using hydrochloric acid failed to visualize the pancreatic duct, (Fig. 15 and 16) but the use of morphine showed that the intact duodenal wall acted as a one way valve and prevented duodenal reflux. Kymographic studies supported these findings (Fig. 11). The patient has been asymptomatic since operation and has gained 18 pounds in weight.

Case No. 2—L.N. (Bellevue Hospital, No. 14276-47) was a 43-year-old female with a 20-year history of recurrent attacks of severe epigastric pain radiating to the back and to left upper quadrant. Investigations of her stomach, duodenum, esophagus, gall bladder, colon and kidneys were all negative except for gastric achlorhydria. A secretin test showed reduced function of the pancreas, (total volume 60 cc, total amylase 18 units). At operation on April 7, 1947, some adhesions around the gall bladder were found. The pancreas was normal to palpation. A chlangiogram failed to visualize the pancreatic duct. Cholecystectomy and endocholedochal sphincterotomy was done. Postoperatively, there was little drainage through the T tube, due to the fact that the distal part of the cross arm was twisted and occluded. A cholangiogram performed immediately after the removal of the T tube showed a narrowed, irregular common duct emptying readily into the duodenum. The pancreatic duct was not visualized.

The patient was well for 2 months, when she developed several attacks of transient epigastric pain lasting 5 minutes. Eight months after operation she had 2 attacks of severe epigastric pain after eating pork chops. At no time was the serum amylase found elevated. She had other complaints,—pain at the cardiac sphincter on drinking water, globus hystericus, urinary frequency. Sectioning of the sphincter in this patient was ill-advised.

Case No. 3—J.S. (Bellevue Hospital No. 18966-47) was a 57-year-old male with a 9-year history of recurrent attacks of severe epigastric pain radiating to the back and both scapulae, associated with marked gaseous distension and lasting on each occasion from 2 to 7 days. A cholecystectomy was performed in this hospital in 1939 for chronic non-calculus cholecystitis. After operation, he developed a wound dehiscense which was repaired. His attacks persisted but observations both on the ward and in the out-patient-department revealed no positive findings. The serum amylase was always low, never rising over 50 mg. %. A secretin test showed normal pancreatic function. By exclusion, a diagnosis of recurrent acute pancreatitis was made. At operation on May 29, 1947 very extensive adhesions of the stomach, duodenum, colon and liver were found. The common duct was very narrow, and the pancreas felt normal to palpation. A cholangiogram, using acid to produce spasm of the sphincter of Oddi, visualized the pancreatic duct. A probe was passed down the common bile duct into the duodenum, and after opening the duodenum, the sphincter was cut under vision. A fine catheter was passed down the common duct into the duodenum and brought out through the wound.

Postoperatively, his wound separated on the 3rd day and a biliary fistula developed, but after a stormy convalescence he was discharged with his wound healed. The patient was seen on the 18th of May, 1948. He had gained 50 pounds in weight; he had no pain; was eating without any restriction and is a completely rehabilitated person.

Case No. 4—J.B. (Bellevue Hospital, No. 26094-47) was a 47-year-old female, first admitted on September 17, 1945 with a 3-week history of recurrent attacks of severe epigastric and right upper quadrant pain, each attack lasting from 3 to 24 hours and accompanied by fever and leucocytosis. At that time a cholecystogram failed to visualize the gallbladder. She was discharged and observed in the out-patient-department. Roentgen ray studies of the stomach, duodenum and gall bladder showed no abnormality except for an irregularity in the duodenum. Typical attacks of pain

persisted. A diagnosis of recurrent acute pancreatitis was made but she was not admitted for operation until, during a very severe attack in May, 1947, the serum amylase was found to be 308 mg. %.

At operation, June 5, 1947, dense adhesions were present around the gall bladder and liver. The pancreas was moderately thickened. The gallbladder was thick and edematous and contained a few small stones. The common bile duct was moderately

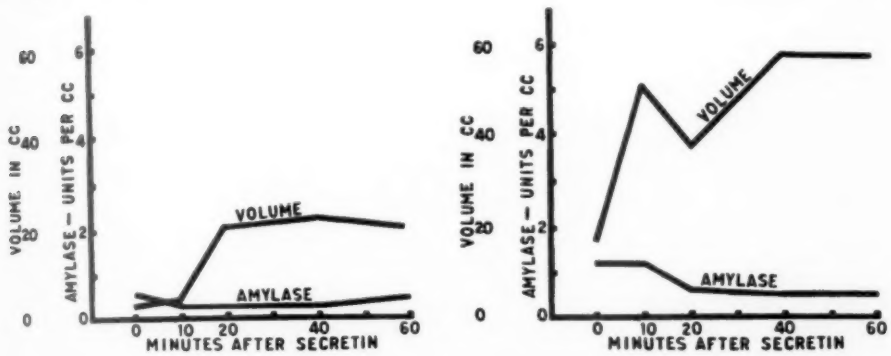

FIG. 14.—(Case 4).

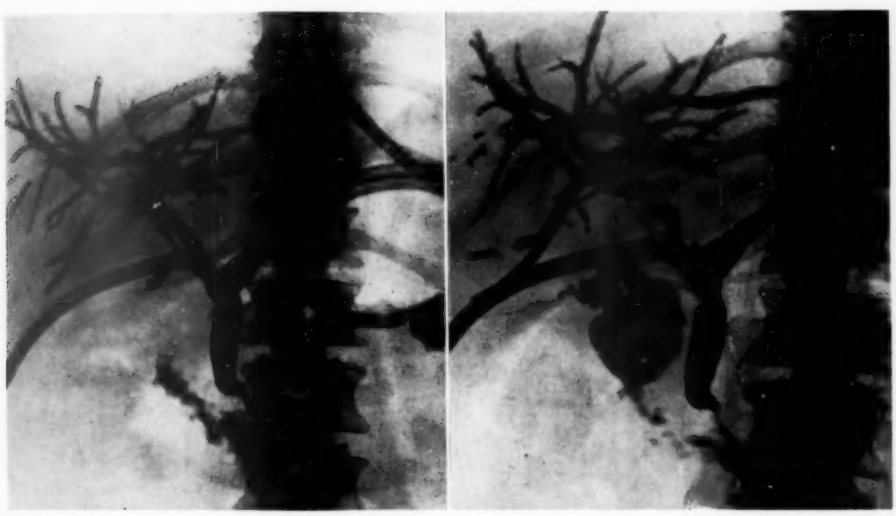

FIG. 15. FIG. 16.

FIGS. 15 and 16.—(Case 1.) Cholangiographic studies two weeks after sphincterotomy, shows the free entrance of contrast medium into the duodenum. (Fig. 15) Following application of acid to the duodenum (Fig. 16), the pancreatic duct is not visualized. Under similar conditions prior to sphincterotomy the pancreatic duct was visualized (Fig. 14.)

dilated. Cholangiographic studies showed that the bile and the pancreatic ducts emptied into a common ampulla a considerable distance from the ampulla of Vater (Fig. 17 and 18). Cholecystectomy and endocholedochal sphincterotomy were carried out. Histologic examination of the gall bladder showed acute and chronic cholecystitis. Biopsy of the pancreas revealed mild fibrosis. Two weeks after operation cholangiographic studies visualized the pancreatic duct presumably due to the fact that the junction of

the two ducts was high in the duodenal musculature (Fig. 19). Following the administration of morphine, the intramural parts of the ducts were compressed by the increased tonus of the duodenum, and the pancreatic duct was no longer visualized (Fig. 19). The secretin test showed marked reduction in pancreatic function (Fig. 14). Kymographic tracings indicated functional destruction of the sphincter of Oddi.

Patient has been asymptomatic since operation except for one attack of mild epigastric distress lasting 10 minutes following the eating of pork sausage. She has gained 20 pounds in weight. A secretin test performed 6 month after operation revealed marked improvement in the pancreatic function (Fig. 14).

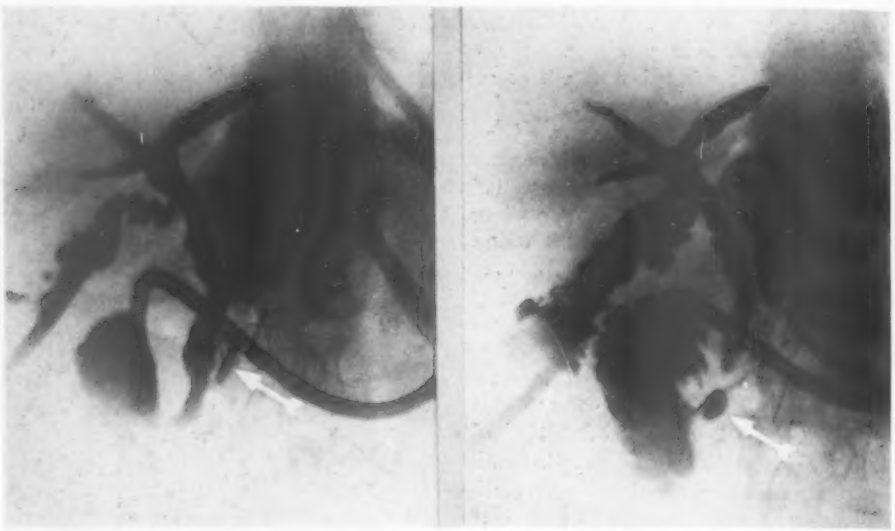

FIG. 17. FIG. 18.

FIGS. 17 and 18.—(Case 4) Operative cholangiogram through the cystic duct. Contrast medium was injected at the same time as hydrochloric acid was applied to the papilla of Vater through a duodenal tube. The pancreatic duct (arrow) was visualized (Fig. 17). Another view (Fig. 18) demonstrated an ampulla (arrow) high in the duodenal wall into which both du.ts emptied.

Case No. 5—W.B., (Bellevue Hospital No. 38441-47) was a 58-year-old male with a 3 months history of epigastric pain radiating to the right upper quadrant and back. This pain was made worse by eating fatty foods. The pain was continuous and superimposed were bouts of very severe pain, vomiting and gaseous distension. Roentgenograms of the stomach and duodenum were normal; gallbladder visualized faintly. At operation on August 18, 1947, the gallbladder, although thin-walled, was adherent by old and fresh adhesions to the omentum, colon and duodenum. No stones were present. The pancreas felt normal. A cholangiogram through the common duct visualized the pancreatic duct (spasm of the sphincter of Oddi produced by hydrochloric acid). On the basis of the dense adhesions and the absence of stones, and the presence of the common passageway, a diagnosis of recurrent pancreatitis was made and the sphincter of Oddi was cut through the common duct. Histologic examination of the gallbladder showed minimal chronic cholecystitis. A cholangiogram 2 weeks after operation did not visualize the pancreatic duct in spite of injection of acid into the duodenum. A kymographic tracing revealed proof of the destruction of the sphincter of Oddi. The secretin test revealed normal pancreatic secretion (total volume 172 cc., total amylase 567 units). Since discharge, the patient has had a feel-

ing of epigastric pressure whenever he is constipated, but no persistent pain or acute attacks.

Case No. 6—M.W. (Bellevue Hospital, No. 40368-47) was a 32-year-old female who was admitted August 23rd, 1947 five days after onset of severe epigastric pain associated with vomiting. Similar attacks had occurred during the previous year. On admission, jaundice was noted (Icteric Index 15) as well as bile and a trace of sugar in the urine. Marked tenderness in the epigastrium and left upper quadrant were present. The serum amylase was 1355 mg. % on August 24th, 514 mg. % the next day, and 56 mg. % 5 days later. A cholecystogram on August 24, 1947 failed to visualize the gall bladder but on Sept. 4, 1947 repetition of the test showed good concentra-

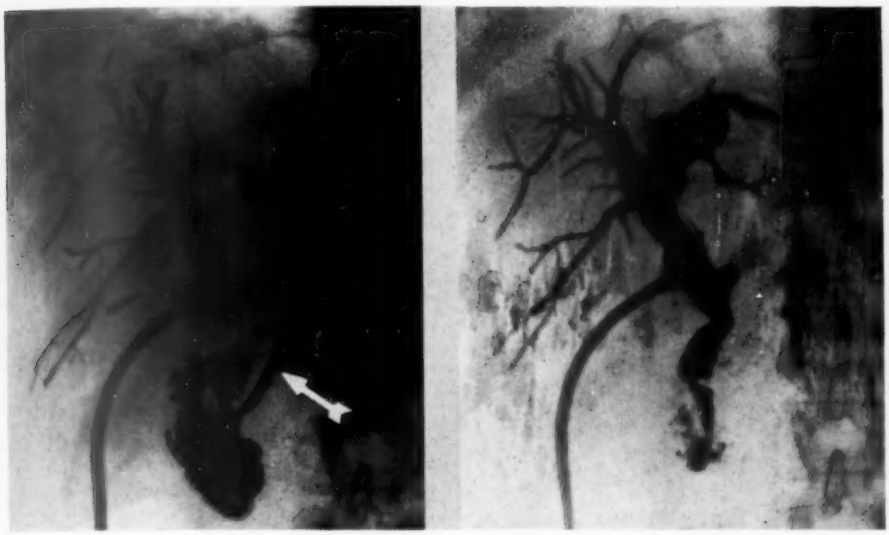

FIG. 19. FIG. 20.

FIGS. 19 and 20.—(Case 4) Cholangiogram done through a T-tube 2 weeks after operation. The pancreatic duct (arrow) was filled with contrast medium (Fig. 19) in spite of section of the sphincter because of an unusually high junction of the bile and pancreatic ducts. Morphine (gr. 1/6) increased the tonus of the whole duodenal wall and compressed the junction of the two ducts, preventing further reflux (Fig. 20).

tion and evacuation. Roentgenogram of the stomach and duodenum showed no abnormality. A secretin test showed normal pancreatic function (total volume 187 cc; total amylase 336 units). At operation on September 11, 1947 after separating adhesions around the liver, the gallbladder was found to be relatively normal; the common bile duct was twice the normal diameter; the pancreas was slightly indurated. A cholangiogram visualized the pancreatic duct. Cholecystectomy and endocholedochal sphincterotomy were performed. Cholangiography 2 weeks later performed through a T tube failed to visualize the pancreatic duct. Kymographic tracings of the resistance of the sphincter of Oddi indicated destruction of its function.

Patient seen on the 18th of May, 1948, gained 15 pounds in weight. Her complaint was that her increase in appetite and unrestricted diet was promoting too rapid gain in weight.

Case No. 7—G.B. (Bellevue Hospital, No. 46408-47) was a 43-year-old female with a 9-year history of recurrent attacks of moderate epigastric pain, lasting from ½ to 1 hour and relieved by vomiting. She had lost 15 pounds in weight because her food intake was restricted, since food brought on the attacks. Her gallbladder had

been removed at another hospital 13 years previously for cholelithiasis. She was admitted to this hospital on May 7, 1947, three days after a severe attack of epigastric pain radiating to the right upper quadrant, fever and vomiting. A serum amylase of 740 mg. % confirmed the diagnosis of acute pancreatitis. Roentgenogram of the stomach and duodenum revealed no abnormality. Patient was discharged and followed in the out-patient-department. Because of daily post-prandial pain and recurrent severe attacks, she was readmitted on October 2, 1947. A secretin test showed normal pancreatic function (total volume 185 cc; total amylase 367 units). At operation, the common bile duct was found moderately dilated; the pancreas firm but not enlarged; a hard mass was palpated in the lesser curvature of the stomach which was opened; a small, deep gastric ulcer was found and excised. A cholangiogram failed to visualize the pancreatic duct, possible due to the fact that the end of the duodenal tube through which the acid was injected was not adjacent to the papilla. The common duct was opened and endocholedochal sphincterotomy performed. A cholangiogram performed 2 weeks after operation through the T tube visualized the pancreatic duct, (Fig. 21). A kymographic tracing, using acid and morphine, indicated destruction of the sphincter of Oddi.

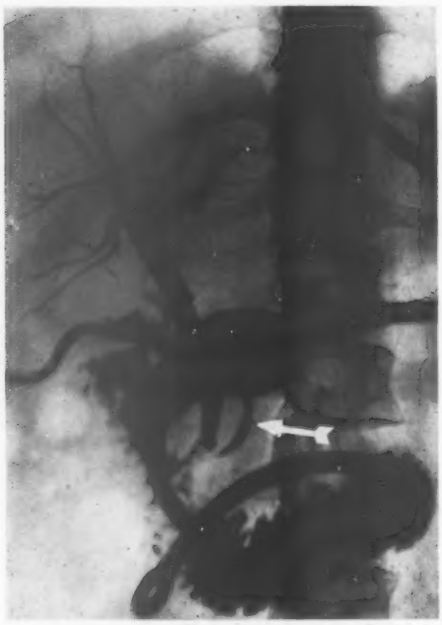

FIG. 21. — (Case 7) Cholangiogram through a T tube 2 weeks after sphincterotomy, visualized the pancreatic duct (arrow). As in Case 4, the high junction of the bile and pancreatic ducts permitted filling of the pancreatic duct in spite of sphincterotomy.

The patient has been symptom free since operation.

Case No. 8—F.R. (Bellevue Hospital. No. 47498-47) was a 27-year-old female with a 3-year history of recurrent attacks of severe, mid-abdominal pain radiating to the epigastrium and left upper quadrant, occurring at varying intervals from daily to monthly, lasting from 2 hours to 1 week and accompanied by fever and tenderness in the epigastrium and left upper quadrant. Her last attack started 5 days before admission to the Third (New York University) Medical Division of Bellevue Hospital, October 9, 1947. Examination at this time revealed (1) jaundice (Icteric Index 22, bile in urine); (2) paralytic ileus (distended small bowel with fluid levels by Roentgen ray); (3) diametes with acidosis (blood sugar 250 mg. F, sugar and acetone in urine, carbon dioxide combining power in blood, 30 volume %); (4) hypertension (B.P. 158/96); (5) albumin in urine; (6) serum amylase over 300 mg. %.

Under treatment by intestinal suction, atropine, intravenous fluids and insulin all symptoms disappeared within 1 week. A cholecystogram 3 weeks after onset of attack visualized the gall bladder. Roentgenogram of the stomach and duodenum showed normal findings. The patient was transferred to the surgical service on November 1, 1947. A secretin test showed diminished pancreatic function (volume 91 cc.; amylase 92 units). At operation on November 7, 1947, a thin-walled gallbladder surrounded by dense adhesions was found; the pancreas was hard, enlarged to at least twice its normal size, and showed areas of old diffuse hemorrhage beneath its capsule. A cholangiogram visualized the pancreatic duct. The common bile duct was very narrow.

After cholecystectomy, the duct was opened and a fine probe passed into the duodenum, which was opened over the probe. The sphincter was sectioned and a fine catheter passed up the bile duct and out through the lateral angle of the wound. The duodenum was then closed. The catheter was dislodged accidentally on the 14th day and a cholangiogram, performed, immediately afterwards through the fistula, visualized the pancreatic duct (Fig. 22). The fistula closed the next day and the patient was discharged 16 days after operation. Histologic examination of a biopsy of the pancreas

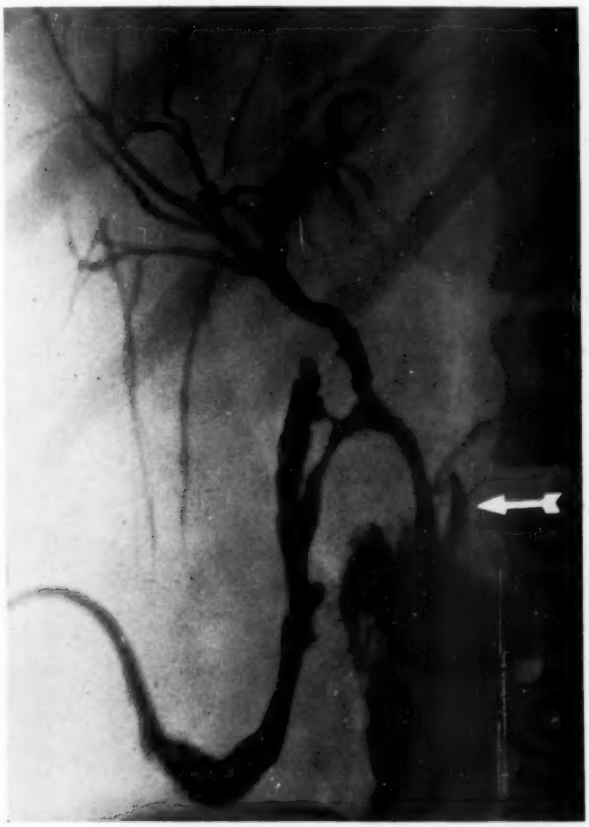

FIG. 22.—(Case 8) Cholangiogram through a fistula two weeks after transduodenal sphincterotomy demonstrated a narrow common bile duct and filling of the pancreatic duct, due to its high entrance into the common duct.

showed a marked inflammatory reaction and replacement of acinar tissue by extensive fibrosis. She has been asymptomatic since operation, in spite of relapsing to old habits of periodic alcoholic sprees. She has gained 20 pounds in weight.

Case No. 9—R.G. (Bellevue Hospital, No. 24620-47) was a 27-year-old female with a 4-year history of recurring attacks of epigastric pain radiating to the back and to both upper quadrants and lasting 10 to 30 minutes. Roentgenogram of the gallbladder showed a functioning viscus with stones. At operation on May 27, 1947, a moderately thickened gallbladder containing many stones was removed. A cholangiogram performed through the cystic duct visualized the pancreatic duct (Fig. 23 and

FIG. 23.

FIG. 24.

FIG. 25

FIGS. 23, 24 and 25.—(Case 9) Operative cholangiogram at first operation (cholecystectomy for chronic calculous cholecystitis) visualized a high junction of the pancreatic duct (arrow) with the common bile duct when the sphincter of Oddi was made spastic by acid (Fig. 23). When the acid was washed away (Fig. 24) the pancreatic duct could not be visualized in spite of the continued injection of contrast medium. The relaxation of the duodenal wall was evident. A postoperative cholangiogram (Fig. 25) through a T-tube after the second operation (transduodenal sphincterotomy) again visualized the pancreatic duct (arrow), a common finding in the presence of a high junction of the bile and pancreatic ducts.

24). The cystic duct was then tied and the abdomen closed. The patient was discharged on the 9th postoperative day; that night she ate fried liver and was readmitted to the hospital during an attack of severe epigastric pain. The serum amylase was 595 mg. %. The symptoms subsided and 2 days later the serum amylase was 176 mg. %. She was discharged and followed in the out-patient-department. She remained well for 5 months and then increasingly severe attacks recurred. At re-operation on December

FIG. 26.—(Case 10). Operative cholangiogram through the cystic duct visualized the markedly dilated common bile duct and a dilated pancreatic duct (arrow). Spasm of the sphincter of Oddi was produced by acid applied to the papilla of Vater.

27, 1947, the sphincter of Oddi was cut transduodenally. A cholangiogram taken 2 weeks after operation visualized the pancreatic duct again (Fig. 25). Following administration of morphine, the pancreatic duct could no longer be visualized. Kymographic tracings indicated destruction of the sphincter of Oddi.

Since discharge from the hospital the patient complains of post-prandial pain lasting from 5 to 10 minutes, gradually decreasing in intensity. She is not symptom free as yet.

Case No. 10—A.W. (Bellevue Hospital, No. 387-48) was a 54-year-old female with an 8-year history of recurrent attacks of mid-abdominal and epigastric pain lasting from 1 to 3 days. She was admitted on December 6, 1947, three days after onset of a severe attack. The serum amylase was 382 mg. %, white blood count 18,000; the abdomen was distended and there was gas and fluid levels in the small bowel by Roentgen ray. There was also marked tenderness in the epigastrium and left upper quadrant. The symptoms disappeared in 2 days and the serum amylase

dropped to 75 mg. % 8 days after onset. The gallbladder failed to visualize, but radio-opaque stones could be seen. A secretin test revealed marked impairment of the pancreatic function (total volume 70 cc.; total amylase 235 units).

At operation, January 5, 1948, the colon, stomach and duodenum were found adherent to the gallbladder which was distended and full of small, black stones. The common bile duct was three times the normal size; the pancreas was firm but not unduly enlarged. Cholangiography visualized the pancreatic duct (Fig. 26). Cholecystectomy and endocholedochal sphincterotomy were performed. The patient de-

FIG. 27.—(Case 12). Postoperative cholangiogram through a T tube in the common bile duct visualized the pancreatic duct for a short distance with a primary branch (arrow). There was a dilatation of the portion of the duodenum proximal to the papilla with narrowing of the distal segment, possibly a factor in the pain this patient experienced after operation.

veloped shock-like symptoms during the operation which persisted with complete anuria until 3 days after operation when she died. The diagnosis of mismatched transfused blood was confirmed by histological examination of a section of the kidney.

Case No. 11—H.W. (Bellevue Hospital, No. 906-48) was a 49-year-old white male, admitted on January 6, 1948. In 1940 a cholecystostomy had been performed for acute gangrenous cholecystitis with stones; the patient was well except for intolerance to fatty foods and post-prandial gaseous distension until November, 1947, when he began to suffer from attacks of very severe epigastric and right upper quadrant pain radiating to the back, often accompanied or followed by periods of frothy diarrhea. In between these attacks he had epigastric pain after almost every meal, and became afraid to eat.

A secretin test on January 6, 1948 revealed marked impairment of pancreatic function (volume 40 cc., total amylase 88 units).

At operation on January 8, 1948, dense adhesions were found at the porta hepatis. The common duct was twice its normal size. The pancreas was enlarged and hard in its entire length. A cholangiogram showed a dilated common duct but failed to visualize the pancreatic duct; no evidence of the previously drained gallbladder could be seen. The common duct was opened and endocholedochal sphincterotomy performed. The common duct was closed and a small drain placed close to it. Convalescent was uneventful and attacks of pain ceased. He has had no diarrhea since

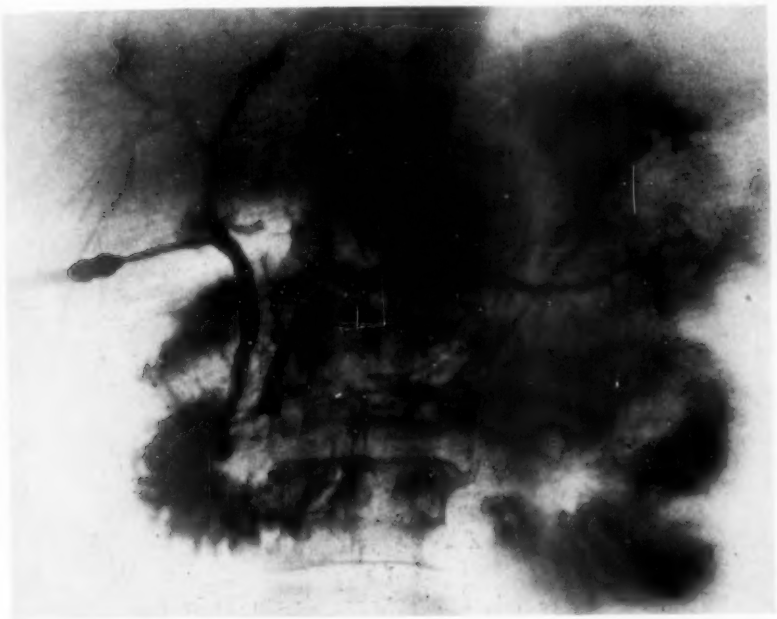

FIG. 28.—(Case 14). Operative cholangiogram through a needle in the cystic duct visualized the whole length of the pancreatic duct (arrows). The bucket of the duodenal tube through which acid was applied, can be seen lying against the papilla.

the operation. However, 3 months later he complained of a steady aching pain in the right side of the abdomen radiating across to the left side. Up to the present time, the cause of this pain has not been determined. A secretin test on May 12, 1948 showed marked improvement in pancreatic function (total volume 88 cc., total amylase 135 units.).

Case No. 12—M.L. (Bellevue Hospital, No. 659-48) was a 34-year-old female who had a chronically inflamed gall bladder with stones removed in 1941. The attacks of severe epigastric pain, radiating to the back and both upper quadrants from which she had suffered for 5 years prior to operation, recurred 9 months after operation and for 6 months had been so severe and so frequent as to incapacitate her. Under observation on the ward she developed 2 severe attacks of epigastric pain associated with marked tenderness in the upper left quadrant. The serum amylase was not elevated. A secretin test revealed normal pancreatic function (total volume 143 cc.; total amylase 497 units). Roentgenograms of the stomach and duodenum showed no abnormality. At operation, January 12, 1948 dense adhesions were found between the liver and the

stomach, duodenum and colon. The pancreas was not unduly indurated. The remnant of the cystic duct, 2" long, was isolated and removed. The common duct was dilated twice its normal size. A cholangiogram failed to visualize the pancreatic duct. The common duct was opened and the sphinchterotome passed to the papilla, but it could not be pushed into the duodenum without undue force. The duodenum was opened and the papilla found tightly contracted. It was dilated and the sphincterotome pushed through under vision and the sphincter sectioned. The duodenum was closed and the common bile duct drained by a T tube. Cholangiographic studies 2 weeks later visualized the pancreatic duct, but showed marked narrowing of the duodenum

FIG. 29.

FIG. 30.

FIGS. 29 and 30.—(Case 14). Cholangiographic studies carried out through a T tube two weeks after sphincterotomy. Sudden painful distention of the common duct with contrast medium failed to produce spasm of the sphincter of visualization of the pancreatic duct (Fig. 29). After morphine injection the cholangiogram demonstrated compression of the terminal part of the common duct by the increased tonus of the duodenal wall, showing that its one-way valve action was intact (Fig. 30).

with dilatation of the first part evidently as the result of opening the duodenum (Fig. 27). Kymographic studies indicated destruction of the sphincteric function.

Since operation, the patient has complained of attacks of transepigastric pain lasting from 5 to 10 minutes, and occurring after meals. When last seen she stated that the attacks have been decreasing in frequency and severity but she still had some tenderness on pressure in the epigastrium.

Case No. 13—D.C. (Bellevue Hospital, No. 43131-46) was a 38-year-old female, first admitted on September 10, 1946, 3 days after onset of an attack of acute pancreatitis associated with jaundice and serum amylase of 256 mg. %. The attack subsided rapidly but recurred following a fatty meal (Fig. 1). A cholecystogram failed to visualize the gall bladder, but several radio-opaque stones could be seen in the region of the common duct. At operation, October 3, 1946, a thick-walled gall bladder filled with stones was removed. The common bile duct was indurated, enlarged and contained 4 stones. A cholangiogram failed to visualize the pancreatic duct but the intravenous injection of secretin was followed by the appearance of pancreatic juice in the common duct, thus proving the presence of a common passageway. It was felt

that the pancreatitis was due to obstruction of the papilla of Vater by a stone and was not due to spasm. Accordingly, the sphincter of Oddi was not sectioned.

The patient was free of symptoms for one year when attacks of epigastric pain recurred and increased in frequency. Roentgenogram of the stomach and duodenum revealed no abnormality. Re-operation January 23, 1948 revealed 3 more stones in the common duct, apparently missed at the first operation. They caused no jaundice but

FIG. 31.—(Case 15). Operative cholangiogram through a needle in the cystic duct failed to visualize the pancreatic duct. The common bile duct was dilated and its retroduodenal course distorted by the calcified pancreas (Fig. 12).

possibly reflex spasm of the sphincter had resulted in recurrent attacks of pancreatitis. A cholangiogram revealed the pancreatic duct emptying into the ampulla low down near the papilla. Palpation of the stomach disclosed a thickening at the lesser curvature on the posterior wall. The stomach was opened and a large, shallow ulcer, 1.5 cm in diameter was seen. It appeared to be benign but a biopsy was taken to confirm this. The opening in the stomach was closed. Endocholedochal sphincterotomy was then performed. Two weeks after operation, a cholangiogram visualized the terminal part of the pancreatic duct. Kymographic studies indicated the destruction of the sphincter of Oddi. Biopsy of the gastric ulcer was reported a benign.

Roentgenological examination on May 11, 1948 revealed a defect in the gastric wall which may be a persistent ulcer (although the patient has been well and gaining weight) or a recurrence.

Case No. 14—O.T. (Bellevue Hospital, No. 12709-47) was a 44-year-old male addicted to alcoholic sprees following which, during the past 3 years, he would develop very severe attacks of epigastric and right upper quadrant pain, abdominal distension and vomiting. He was admitted to a number of different hospitals for this condition but no accurate diagnosis was made until, during an admisson to Bellevue Hospital in March, 1946, a diagnosis of recurrent acute pancreatitis was made on the basis of serum amylase determinations (Fig. 36). Roentgenogram of the gall bladder, stomach and duodenum showed no abnormality. He left the hospital when his symptoms subsided but, after several more attacks, returned for operation. A secretin test

FIG. 32.—(Case 19). The cholecystogram demonstrated a normal gallbladder and calcification in the head of the pancreas (arrow). The tube visible in this film lay in the pancreatic fistula to the skin.

showed normal pancreatic function (total volume 271 cc.; total amylase 638 units).

At operation on Feb. 11, 1948 dense adhesions were found between the liver and the adjacent organs. The gallbladder was thin-walled and contained no stones. The pancreas was firm. The common duct was normal in diameter. A cholangiogram visualized the whole pancreatic duct (Fig. 28). Cholecystectomy and endocholedochal sphincterotomy were performed. Cholangiographic studies 2 weeks after operation failed to visualize the pancreatic duct under spasm of the sphincter produced by pain (Fig. 29). After morphine administration, the function of the intact duodenal wall as a one-way valve could be seen to be intact (Fig. 30). Kymographic studies were further evidence of destruction of the sphincter of Oddi.

The patient had no further attacks of pancreatitis as observed during subsequent hospital admission for alcoholism.

Case No. 15—F.J. (Bellevue Hospital, No. 4485-48) was a 50-year-old male with a 13-year history of attacks of severe upper mid-abdominal pain, radiating to the epigastrium and left upper quadrant, lasting 2 hours to 2 days and occurring 2

to 3 times a month. These attacks followed a big meal and were most severe if food were taken after a prolonged alcoholic spree. There was no history of diarrhea. Roentgenograms of the abdomen revealed widespread calcification of the pancreas (Fig. 11); X-ray of the gall bladder showed normal visualization; and of the stomach and duodenum was reported as suggestive of duodenal ulcer. The glucose tolerance curve was normal. A secretin test showed diminished volume response of pancreatic juice flow but fairly good amylase concentration (total volume 105 cc.; total amylase 297 units). Since the symptoms were similar to those of non-calcified recurrent acute pancreatitis, and since he had good external and internal pancreatic function, it was decided to treat him as recurrent acute pancreatitis.

At operation, February 19, 1948, only a few adhesions were present at the fundus and ampulla of the gallbladder which was thin-walled. The pancreas was markedly enlarged throughout, very hard, and with cobble-stone-like surface. The head of the pancreas pushed the duodenum forward and distorted it. A thin scar on the anterior duodenal wall was suggestive of a healed duodenal ulcer. A cholangiogram showed an enlarged common bile duct with distortion due to pressure from the pancreas, but the pancreatic duct was not visualized (Fig. 31). The gallbladder was removed and the common duct opened. Due to difficulty in passing the sphincterotome through the papilla, the duodenum was opened and the instrument passed through under vision. The blade was then opened, retracted and the sphincter sectioned. Two weeks after operation, cholangiographic studies again failed to visualize the pancreatic duct. Kymographic studies showed a slight response to acid indicating possibly incomplete section of the sphincter but the response to morphine showed excellent functional destruction (Fig. 13). The patient has had no symptoms since operation but the acid test of an alcoholic bout has not yet been applied.

Case No. 16—C.R. (Bellevue Hospital, No. 7790-48) was a 29-year-old female with a 6-year history of recurrent monthly attacks of severe epigastric pain associated with nausea and vomiting, and radiating to both upper quardrants and to the back. Repeated Roentgenograms of the gallbladder, stomach and duodenum showed no abnormality. Exploratory laparotomy at another hospital during an acute attack in 1943 revealed acute pancreatitis. Cholecystostomy and drainage of the pancreas were performed. Drainage from the cholecystostomy site persisted intermittently for the intervening 5 years and, at one time during the course of this biliary drainage, a small cholesterol stone was extruded. When the fistula closed the attacks recurred.

She was admitted to this hospital on February 15, 1948. Contrast medium injection of the fistula revealed a small cavity which appeared to hold a radio-translucent stone. The drainage fluid contained no amylase. A secretin test showed marked reduction in the pancreatic function (total volume 42 cc.; total amylase 43 units). At operation on February 25, 1948, the fistula was found to communicate with a markedly fibrotic gallbladder containing a stone impacted in the cystic duct. The common bile duct was at least twice its normal size. The pancreas was hard throughout and moderately enlarged. A cholangiogram visualized the whole pancreatic duct (Fig. 10). Cholecystectomy and endocholedochal sphincterotomy were performed. The common duct was closed and a small drain, which was removed 4 days after operation, placed down to it.

Patient has been completely symptom free since operation.

Case No. 17—J.D. (Bellevue Hospital No. 8639-48) was a 32-year-old male with a 5-year history of frequent recurrent attacks of severe upper abdominal pain, sudden in onset, originating in peri-umbilical region and spreading up to the epigastrium and both upper quadrants and to back, accompanied by nausea and vomiting (bloody on 2 occasions) and lasting from 2 to 3 weeks. No diarrhea following these attacks. In November, 1946, a cholecystectomy was done but the attacks persisted. In 1947, at another hospital, a diagnosis of acute pancreatitis was made (serum amylase

FIG. 33.

FIG. 34.

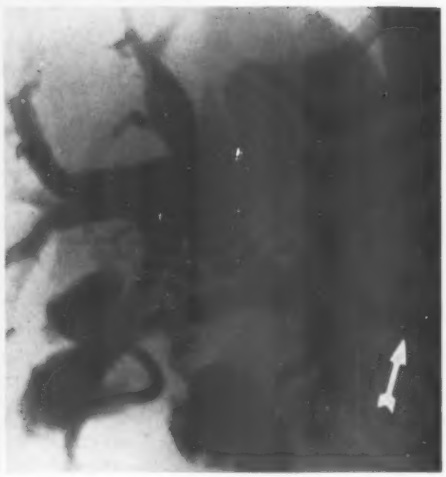

FIG. 35.

FIGS. 33, 34 and 35.—(Case 19). Postoperative cholangiogram showed the catheter passing down the common bile duct into the duodenum (Fig. 33). Following partial withdrawal of catheter, the distorted narrowed common bile duct could be visualized (Fig. 34). A long thin shadow (arrow) to the right of the common duct might be the pancreatic duct but the distortion due to calcification of the head of the pancreas made this uncertain. Following administration of morphine (Fig. 35) the terminal part of the common duct was constricted by the increased tonus of the duodenal wall. The tube (arrow) lying in the pancreatico-gastrostomy was visualized.

281 mg. %) and confirmed by exploratory laparotomy. In February, 1948 a similar attack (amylase 209 mg. %) was observed. He was admitted to Bellevue Hospital February 19, 1948 at which time gastro-intestinal Roentgenolic findings were normal. Secretin test showed diminished function (total volume 132 cc.; total amylase 135 units). At operation on March 4, 1948, dense adhesions were found in the upper abdomen. The common duct was dilated 3 times its normal size; the pancreas was hard and enlarged throughout. An operative cholangiogram was unsatisfactory and failed to reveal the pancreatic duct. The common duct was opened and the sphincterotome passed. The duodenum was then opened and the sphincter of Oddi sectioned by the sphincterotomy under vision. The duodenum was closed and a T tube placed in the common duct.

Two weeks after operation a kymographic tracing showed evidence of destruction of the sphincter (no response to acid and diminished response to morphine). A cholangiogram showed ready entrance of contrast medium into the duodenum and failed to visualize the pancreatic duct. The T tube was removed on March 24, 1948 and the patient was discharged. He has had no symptoms since operation.

Case No. 18—J.W. (Holy Name Hospital, Teaneck, N. J., operation with Dr. Walter J. Farr) was a 53-year-old male with a 6-year history of attacks of right upper quadrant pain lasting 8 to 10 minutes. In 1944 a cholecystectomy was performed for stones. He was well for 6 months when extremely severe attacks in the right upper quadrant recurred, lasting from 10 minutes to 6 hours, and occurring 2 to 3 times a week. A diagnosis of recurrent acute pancreatitis was made. At operation, the pancreas was found to be enlarged and rock-like in consistency throughout its whole extent. The common bile duct was about 3 times its normal diameter with a thickened inflamed wall. Endocholedochal sphincterotomy was done and the common bile duct closed. A small rubber drain was placed down to the duct and removed 3 days later.

The patient has been free of symptoms since operation.

Case No. 19—J.G. (Bellevue Hospital, No. 906-48) was a 36-year-old male admitted to the psychiatric division of Bellevue Hospital on February 24, 1948 in a semi-stuporous condition due apparently to insulin hypoglycemia. He had a history of attacks of severe epigastric pain radiating to the back for 11 years. In 1940 an operation, cholecystostomy and drainage of a pancreatic cyst for obstructive jaundice due to the cyst, was performed. After 2 years the attacks of severe epigastric pain recurred and he became a morphine addict. In 1945, at another hospital, following studies which indicated marked diminution of pancreatic function, an attempt to do a pancreatectomy was abandoned and a splenectomy and drainage of a pancreatic cyst was carried out. He developed a persistent pancreatic fistula and attacks of epigastric pain persisted. After this operation a pancreatic-colic fistula was demonstrated but this apparently closed. At this time, the patient developed diabetes for which he required 40 Units of Insulin. He continued to have attacks of severe pain associated with paralytic ileus on occasion.

Studies at Bellevue Hospital revealed a severe diabetes (glucose tolerance curve: 173,235,333,308 mg. % sugar at ½ hour intervals). Injection of the pancreatic fistula visualized part of the pancreatic duct and showed free communication with the duodenum. Roentgenogram of the stomach and duodenum revealed a normal stomach with some obstruction of the duodenum. Secretin tests could not be done due to failure to pass a duodenal tube. Roentgen-ray studies revealed a normal functioning gallbladder as well as calcification in the head of the pancreas (Fig. 32). He required frequent injections of demerol for pain and to alleviate morphine withdrawal symptoms.

At operation on April 5, 1948 the stomach, duodenum and colon were found to be adherent to the liver. The gallbladder was surrounded by dense adhesions. The pancreatic fistula communicated with the body of the pancreas which was thickened and fibrosed with the head hard, irregular and enlarged. Many large veins coursed around

and over the gastrohepatic omentum, duodenum and pancreas. The common duct was located only after a cholangiogram was done through the cystic duct following removal of the gallbladder. The common duct was wide above and tortuous in its passage behind the head of the pancreas. The pancreatic duct was not visualized. The common duct was opened and a fine probe passed into the duodenum. The duodenum was opened and the sphincter of Oddi was cut transduodenally over the probe. A fine catheter was passed into the duodenum through the bile duct and brought out at the lateral angle of the wound. The pancreatic fistula was excised. The opening which remained in the main pancreatic duct was anastomosed to the overlying stomach over a small rubber tube. Cholangiograms taken 2 weeks after operation showed ready entrance of the contrast medium into the duodenum (Figs. 33 and 34). Following injection of morphine the duodenal musculature was shown to be intact (Fig. 35). Patient

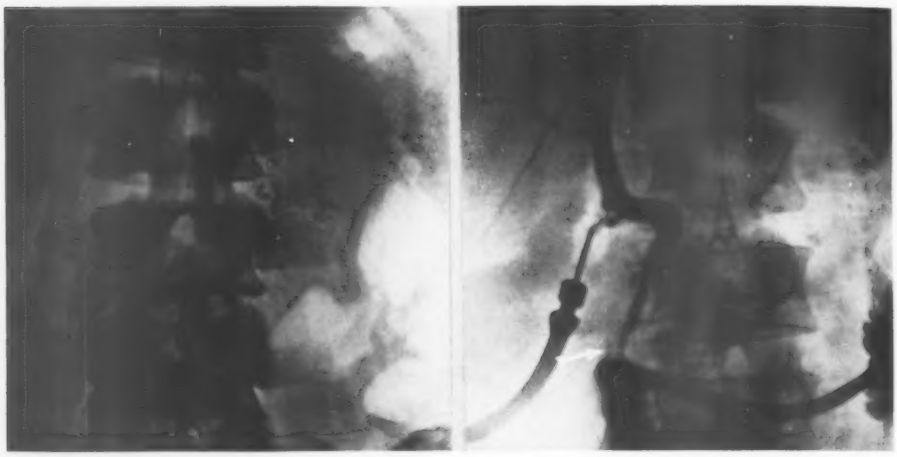

FIG. 36. FIG. 37.

FIGS. 36 and 37.—(Case 21). Calcification of the pancrease (Fig. 36) and operative cholangiogram through a needle in the cystic duct (Fig. 37). The angulation and narrowing of the bile duct in its passage behind the calcified head of the pancreas was noteworthy. A questionable shadow (arrow) may be the pancreatic duct.

has been asymptomatic since discharge, requiring no demerol and the pancreatic fistula has remained closed.

Case No. 20.—D.P. (French Hospital No. 138622) was a 31-year-old female with a 12-year history of attacks of epigastric pain radiating to the back over the 10th rib and to the left upper quadrant. The post-prandial pain has become so frequent that fear of eating led to a loss of 16 pounds in the last 6 months. Appendectomy was performed 12 years ago, and the removal of the right cystic ovary 6 years ago, without alleviating attacks. Complete physical and Roentgen-ray examinations at various hospitals failed to establish any diagnosis. A secretin test showed over 50% loss in pancreatic function (total volume 66 cc.; total amylase 325 units). On the basis of this test and the history, a diagnosis of recurrent acute pancreatitis was made. At operation on April 9, 1948, the gallbladder was found to be normal with only a few adhesions to the ampulla. The pancreas felt normal; the common bile duct was about twice its normal size. A cholangiogram was unsatisfactory owing to technical reasons. The gallbladder was removed and the common duct opened. The tip of the sphincterotome was arrested at the papilla and the duodenum was opened. The tip of the instrument was found arrested in a rather large ampulla of Vater due to the fact that the direc-

tion of the papilla was at right angles to the common duct. The instrument was pushed through the papilla and the sphincter of Oddi cut. When this was done the mouth of the pancreatic duct could be seen opening on the posterior wall of the ampulla 6 mm. above the papilla. A probe could be passed up the pancreatic duct for a distance of 8 cm. The common bile duct and the duodenum were closed and a small drainage tube placed down to that site; this was removed 3 days later. The patient has been asymptomatic since.

Case No. 21—D.R.W. (Beth Israel Hospital, Newark, N. J.—operation with Dr. A. Abrams) was a 40-year-old white male with a 12-year history of attacks of severe epigastric pain radiating to the back and to both upper quadrants, occasionally accompanied by vomiting. The attacks lasted from 2 hours to 2 days and at first occurred about every 6 months, but in the last few years the severe attacks occurred every few weeks and he had pain after eating almost every day. Ten years ago a diagnosis of perforated ulcer was made but no operation was done. Between 1940-1944 he was admitted to 4 different military hospitals. Many roentgenograms showed a normal gallbladder and normal stomach and duodenum. He was finally discharged from the army February 11, 1948 because of incapacitating pain. No diagnosis was made. Examination by a civilian physician revealed calcification of the pancreas (Fig. 36). A cholecystostomy was performed but by request of the patient the pancreas was not removed. He had no pain as long as the cholecystostomy was functioning. As soon as the drainage tube was removed the attacks of pain recurred. A secretin test done on April 12, 1948 revealed marked impairmnt of the pancreas (total volume 120 cc.; total amylase 65 units). At operation on April 16, 1948 the pancreas was found to be large and very hard with an irregular knobby surface. The gallbladder was removed. A cholagiogram visualized the pancreatic duct only questionably (Fig. 37). The common bile duct was about twice its normal size, and very tortuous, owing to its passage behind the enlarged irregular head of the pancreas. The common duct was opened, the sphincterotome passed into the duodenum and sphincterotomy done. The common duct was sutured and a small drain placed down to the line of suture. He has been asymptomatic since operation.

DISCUSSION

The definitive surgical attack on acute recurrent pancreatitis accepts as its basis that when a common passageway between bile and pancreatic ducts can be demonstrated this anatomic arrangement permits the inception of the disease. It may be possible for other unknown mechanisms, not involving bile in the pancreatic ducts, to cause inflammation of the gland. Pancreatitis occurs in mumps and possibly in other virus diseases. Unaltered bile in the pancreatic duct may be innocuous; the anatomic possibility may be present without reflux ever actually occurring. In this conception, there are these conditions necessary for the occurrence of an attack: a common passageway; bile which has been rendered noxious by concentration of its salts or some other change; and spasm of the sphincter of Oddi.

A common passageway can be demonstrated by operative cholangiography or the presence of pancreatic juice in the gallbladder or common duct. That bile which is concentrated by the gallbladder is a likely chemical agent which is injurious to the pancreas is in part attested by the fact that cholecystectomy is frequently a temporary relieving measure.[4, 10, 11] The history of patients may reveal a period of freedom from pain after removal of a functioning

gallbladder without stones. Eventually, however, in some of these patients pancreatitis will occur. The sphincter of Oddi is the sealing mechanism which raises the pressure in the common system by recurrent spasm. This spasm can be induced by hydrochloric acid applied to the papilla. As with other muscular elements of the upper gastro-intestional tract the contraction of the sphincter muscle is also controlled by nervous influences and possibly by hormones. Emotional disturbance or pain can induce spasm. In this sense dysfunction may be related to a similar dysfunction resulting in peptic ulcer or pylorospasm.

An unsolved aspect of this problem is how the bile can enter the pancreatic duct against the secretory pressure of the pancreas itself. Under the stimulus of secretin the flow of pancreatic juice will not permit bile to enter the pancreatic duct. Under the stimulus of ingested food bile pressure and pancreatic juice pressure are the same.

SUMMARY

Methods of diagnosis of recurrent pancreatitis by serum amylase determinations, pancreatic response to secretin stimulation, cholangiograms and biliary tract pressure recordings have been discussed. The etiologic factors first suggested by Archibald of spasm of the sphincter of Oddi in the presence of a common biliary-pancreatic passageway and reflux of bile into the pancreas have been studied on human patients. A summary of patients so studied and treated is presented. These studies confirm Archibald's opinions.

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Discussion.—Dr. Henry Doubilet, New York: I want to thank the members of the Association for the great honor and privilege of the floor. There are two points I should like to make. One is that this series of patients who have been operated on, forms only a small number of the total patients studied. In all routine biliary tract surgery a cholangiogram is done on the operating table. During this procedure normal tenth hydrocholic acid is applied to the papilla of Vater to produce spasm. These cholangiograms are valuable not only for the detection of common duct stones or malignancy, but also to determine the incidence of a common passageway and a reflux mechanism. A large proportion of these patients have been found to have a common passageway. Three of the patients in whom reflux mechanism was

demonstrated by operative cholangiography, since developed recurrent acute pancreatitis. One of these patients had a severe attack nine days after discharge, with an elevated serum amylase. She was finally readmitted and operated upon, at which time the sphincter of Oddi was cut. The other two patients are being followed in the outpatient department until such time as we can find an elevated serum amylase during one of their attacks.

The second point that is of great interest to us, is the relation of the reflux mechanism to the etiology of acute necrotizing cholecystitis or cholangeitis with or without stones. The presence of pancreatic enzymes in the gallbladder or in the common duct is proof of reflux in these patients. We hope to have adequate studies in a few years to support a planned surgical approach in the therapy of these patients; that is, section of the sphincter of Oddi to prevent reflux.

Dr. Alton Ochsner, New Orleans: This work is indeed stimulating. I regret that Dr. Gage is not here to discuss it because, as you know, he has been interested in the treatment of acute pancreatitis by sympathetic block, and I would like to give you some of the results on his cases, and also raise the question of whether in these acute recurrent pancreatitis attacks, in which Dr. Mulholland has shown that section of the ampulla has so dramatically relieved them—it would not be better to perform a plastic procedure on the duct rather than trans-choledocho section. Only time will tell whether this will give rise to stricture later. We have had two patients in whom we have done plastics on the duct, making an incision transductally and then suturing the ductal mucosa to the duodenal mucosa.

(slides) In the 15 cases Dr. Gage has had, typical splanchnic block has been done, using the Kappis technic. This technic consists of choosing a point 7 cm. lateral to the 12th spinous process at the lower border of the 12th rib. The needle is introducted at an angle of 45° until it strikes the body of the vertebra. The direction of the needle is slightly changed so that it can slide just beyond the body of the vertebra. The point of the needle lies in the retroperitoneal space where 15 cc. of ½ to 1 per cent novocain are injected on each side; two similar points are chosen 7 cm. caudad to the first two points and needles are similarly introduced. In all, four injections are made.

Dr. Gage is of the opinion that acute pancreatitis usually occurs when the choledochus and pancreatic duct open conjointly into the ampulla of Vater and that, as a result of obstruction of the communal duct, either by stone or spasm, reflux of bile into the pancreatic duct can occur which may produce acute pancreatitis by activation of the tryptic ferment and also by causing rupture of the pancreatic acini because of the markedly increased pressure within the pancreatic ducts. Because of the extensive fat necrosis associated with acute pancreatis there is considerable demand for calcium to saponify the fat which results in decrease in blood calcium. For this reason, Dr. Gage is of the opinion that patients with acute pancreatitis should be given calcium intravenously. The hypocalcemia does not occur immediately after the attack but is most marked approximately a week after the onset of acute illness. Penicillin is given in order to prevent infection of the necrotic areas.

Dr. H. F. Graham, Brooklyn: I should like to comment on the papers of Dr. Cole and Dr. Mulholland. You will recollect that Dr. Cole mentioned that in about 25 per cent of cases they were not postoperative strictures according to his analysis. Dr. Mulholland mentioned the reflux from the biliary tract into the pancreas, and Dr. Doubilet has also shown that their studies have proved there is a reflux of pancreatic juice into the biliary tract. The cases that follow operation are tragic and distressing, but they are also controversial and subject to differences of opinion. We know of one case, however, an adult who had not been jaundiced previously, which eliminated the congenital aspect. He developed a chronic jaudice without previous

operation, was operated upon and complete obliteration of the common duct and the duct into the liver was found. It is going to be more difficult to prove that these cases are due to reflux of pancreatic juice than in the cases Dr. Mulholland demonstrated as due to reflux of bile, but I think some day this explanation will be accepted as the only rational explanation of many cases of stricture that occur. That can be determined usually by the extent of the stricture, which is much longer than the strictures found from operative interference. The upper end of the common duct is usually dilated after operative damage, while in these cases it is not.

Dr. Evarts Graham, St. Louis: How long after cutting the sphincter does the paralysis last?

Dr. John H. Mulholland, New York (closing): In reply to Dr. Ochsner's suggestion that a plastic operation on the sphincter mechanism might be advisable, I think it is vital to preserve the oblique passage of the common bile duct in the duodenal wall. The muscular intestinal wall containing the intramural portion of the common duct acts as a sphincter and is an effective bar to the reflux of duodenal contents in the biliary tract. None of these patients have developed cholangitis.

In answer to Dr. Graham, we know that our oldest patient, 18 months post-operative, has no evidence of sphincter spasm. Dr. Doubilet, who has done the basic experimental work concerned in this problem, has sacrificed dogs two years after the sphincter was cut and found it retracted and incompetent.

OBSERVATIONS ON SOME METABOLIC CHANGES AFTER TOTAL PANCREATODUODENECTOMY*

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EXPERIENCE WITH TOTAL PANCREATECTOMY has been too meager to allow a judgment of the ultimate usefulness of this procedure. Nevertheless, two statements concerning its future may fairly be made, namely, that the operation is a theoretically sound and promising one, and that its technical difficulties in themselves will not be an insurmountable obstacle to its wider popularity. Indeed, the factor that will most likely decide the fate of this procedure will be our ability or inability to learn to deal satisfactorily with the complex problems that arise in the postoperative management of the patients who have been subjected to it.

Total pancreatectomy is unlike other surgical procedures of similar magnitude in that it brings about profound changes in the physiologic processes of the human organism—changes that, unless they are corrected, are inherently progressive and fatal. In spite of the many valuable lessons learned from animal experimentation, our understanding of the physiologic behavior of the patient recently deprived of his pancreas is quite incomplete. An inadequate grasp of the problem of altered physiological response after total pancreatectomy has undoubtedly been the cause of many fatalities. This certainly has been the case in our experience. Conversely, an increase in the survival rate and a broadening of the usefulness of the operation will eventually come from a more thorough comprehension of the manner in which the human organism responds to removal of the pancreas.

Among the 17 cases of total pancreatoduodenectomy mentioned in medical literature[1-12] only seven lived long enough to allow postoperative investigations. Six of these have been described in detailed accounts by Priestly *et al.*,[2] Brunschwig *et al.*,[3, 6, 7, 8] Whipple,[9] Waugh *et al.*,[10] Dixon *et al.*,[11] and Clagett.[10] The report by Dixon, Comfort, Lichtman and Benson on the metabolic changes in a case of total pancreatectomy is unrivalled for thoroughness and richness of information.

In the present study certain observations on the postoperative course of three cases of total pancreatoduodenectomy of relatively long survival will be reported. These cases have not been described before, although Case 1 has been briefly referred to by McClure.[4]

SHORT SUMMARIES OF THE CLINICAL HISTORIES

For better evaluation of the data to be presented, brief summaries of the clinical histories of the three cases will be first given.

Case 1.—(M.A.S. Case No. 76,836). Male, aged 43 yrs.—Admitted on *January 2, 1944,* with the complaint of intermittent griping distress across the mid-abdomen

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of two weeks' duration. Ease of fatigue, loss of appetite and loss of 20 lbs. of weight during the 8 weeks before admission. Clay-colored stool and dark urine for five weeks. Negative past and systemic histories.

Physical examination: Comfortable. Nutritional state fair. Markedly icteric. T.P.R. normal. B.P. 110/80. Liver palpable 6 cm. below the rt. costal margin, smooth and slightly tender. Gall bladder not palpable. The remainder of the examination essentially negative.

Laboratory findings: Kline exclusion test: negative. Urinalysis: positive for bile, otherwise negative. Routine and warm-stage stool examination: bulky and containing undigested meat; bile present; otherwise negative. The rest of the data of interest are listed in Table I. *Biliary drainage:* no B-bile; cholesterol crystals and clumps of w.b.c. *Roentgen-ray studies:* Serial films of the stomach and barium enema film: negative.

Hospital Course: Diagnosis: Obstructive jaundice caused by carcinoma of the head of the pancreas. *Operation (January 14 1944):* Total pancreatoduodenectomy; splenectomy; gastrojejunostomy and choledochojejunostomy. *Pathologic diagnosis:* Duct carcinoma of the pancreas, G. 2. *Postoperative recovery:* persistence of jaundice, some delay in emptying of the stomach and development of anasarca of moderate degree; slow but steady improvement. Discharged on the 23rd postoperative day in good general condition, weighing 137 lbs, on a diet of carbohydrates 200 Gm., protein 120 Gm. and fat 60 Gm., and on a daily medication consisting of pancreatin (U.S.P.) 3.0 Gm., protamine zinc insulin, 26 U., regular insulin p.r.n. and preparations of vitamin B, C and K.

Course after discharge: From *February 6 to April 23* seen at weekly and bi-weekly intervals in the out-patient clinic. Symptom-free. Diabetes under satisfactory control with 26 to 28 U of protamine zinc insulin. Between *April 23 and 30, 1944,* admitted for studies. (Results shown in Table II.) From *April 30, 1944* until *November 11, 1944,* seen at bi-monthly intervals. During this time, symptom-free; body weight 130-135 lbs.; diet on *September 5, 1944,* changed to C. 300, P. 135, F. 100; insulin increased to 40 U. protamine zinc insulin per day. One or two normal stools daily; 0.32 Gm. pancreatin (U.S.P.) t.i.d.; carrying on half-time work as salesman. On *November 11, 1944,* patient admitted with the complaint of intermittent low-abdominal cramps of a few days' duration; physical examination negative. Serial roentgen-ray films of the small bowel: pressure defects in the contour of stomach and duodenum probably due to extraneous tumor masses. *Diagnosis:* partial acute small bowel obstruction caused by metastatic carcinoma. After discharge on palliative medication on *November 28, 1944,* patient was lost sight of until *March 10, 1945,* when he returned with severe symptoms and signs of intestinal obstruction. He died on *March 12, 1946,* fourteen months after his pancreatectomy. An autopsy was performed, the important findings of which were as follows: Carcinoma of the pancreas (surgically removed). Metastatic carcinoma of the retroperitoneal lymph nodes, peritoneum and liver. Partial obstruction of jejunum by metastatic carcinoma. Peptic ulcer of jejunum at gastrojejunostomy. Small pulmonary emboli.

Case 2.—(A.S., Case No. 518,005). Female, aged 57 yrs.—Admitted on *August 30, 1947,* with the complaint of "yellow jaundice." Onset four weeks earlier of yellow color of skin, attacks of diarrhea with foul and bulky stools of light color associated with transient low-abdominal cramps. Loss of 38 lbs. of weight in four months. Diabetes of eight years' standing; poorly controlled with 24 U. of regular insulin daily. Hysterectomy in 1939.

Physical examination: comfortable, underweight, markedly jaundiced. T. 98.8, P. 78, R. 18. B.P. 120/70. Diabetic retinopathy, O.D. Liver palpable 4 cm. below right costal margin, gall bladder questionably palpable. Generalized arteriosclerosis.

TABLE I.—*Preoperative Determinations of Hemoglobin, Erythrocytes, Leucocytes, Blood Chemistry, Icterus Index, Liver Function and Blood Enzymes.*

	Case 1			Case 2			Case 3		
	Low	Median	High	Low	Median	High	Low	Median	High
Hemoglobin, Gm. %		13.7		10.4	10.6	10.8		11.8	
Erythrocytes, million per cu. mm.		4.37		3.24	3.32	3.44		3.78	
Leucocytes, thousand per cu. mm.		5,750		5,400	7,250	9,100		7,200	
Blood sugar (fasting), mg. %		111		80	188	267	85	143	278
CO_2 capacity, vol. %								53	
NPN, mg. %		31		17	20	23		28	
Chlorides, as NaCl, mg. %							453	456	460
Albumin/Globulin, Gm. %					4.05/2.38			3.28/2.93	
Prothrombin, % normal	40	70	106		75 - 95			80	
Cholesterol, mg. %					276		746	863	980
Cholesterol esters, % of total cholesterol					62				10
Icterus Index, unit	46	81	102	106	119	124	80	94	108
Bilirubin, direct, mg. %					8.27				
Bilirubin, total, mg. %					14.12				
LIVER FUNCTION TESTS									
Cephalin Cholesterol		Neg.		+	++	++++		Neg.	
Thymol Turbidity, unit				0	+	+		Neg.	
Thymol Flocculation				0	0	0		Neg.	
Hippuric acid, oral, Gm.		2.6		0.87	1.36	1.86			
Alkaline Phosphatase, unit				21	22	23			
Lipase, unit								1.4	

NOTE: In this and the following tables the methods of determination were as follows: bilirubin, Malloy-Evelyn; bromsulphalein, Gaebler; calcium, Clark-Collip; CO_2, Van Slyke (volumetric); chlorides, Whitehorn; cholesterol and cholesterol esters, Bloor-Knudsen; diastatic activity (amylase), Myers-Free-Rosinski; icterus index, Meulengracht-Breh; lipase, Cherry-Crandall; N.P.N., Folin-Wu; alkaline phosphatase, Bodansky; phosphates, Fiske-SubbaRow; potassium, Gaebler; albumin and globulin, Howe; prothrombin, Quick; sodium, Kramer-Gittlemen; sugar, Folin-Wu (photoelectric); total fat, Bloor (oxidative); urea nitrogen, Van Slyke-Cullen; urinary nitrogen, Kjeldahl; stool nitrogen, Kjeldahl; blood acetone, Behre-Benedict; urinary acetone, Van Slyke.

TABLE II.—*Postoperative Determination of Blood Hemoglobin, Blood Chemistry, Icterus Index, Liver Function and Blood Enzymes.*

Case 1

TYPE OF DETERMINATION	POSTOPERATIVE DAY																POSTOPERATIVE WEEK		
	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	12	40	65
Hemoglobin, Gm. %			10.5	10.0	10.0		9.0	9.0		9.0	7.9			11.0		11.0		13.9	
Sugar (fasting), mg. %	270	118	138	162		222	270	266	224	358	262	180		208	104	258	70	133	143
CO_2 Capacity, vol. %	47	53	67	74		67	85	70		47	59	46	45		54	53	63	63	
NPN, mg. %										35								38	
Chlorides, as NaCl, mg. %	457		427	435			400	493	445	457	453	493		480	487	413		392	
Total Protein, Gm. %								4.5				3.9		4.7					
Sodium, mg. %			331				339		339	334		328		305	316	316	302		
Phosphorus, mg. %																		3.44	
Albumin/Globulin, Gm. %											2.31/2.25							4.16/2.28	
Prothrombin, % normal							20	45	100	100								95	
Total Lipids, mg. %					559	687	709	563	675	593	583		683	518	563		450	390	
Cholesterol, mg. %																	115	188	
Icterus Index, unit	78			102	98	96	80	69	32	55	36	26	26	25	25	23			
Cephalin Cholesterol														3+				1+	
Amylase, unit			4.0	3.0		2.3		8.5		10.0	8.7	4.3			6.4	9.6		11	

Laboratory finding: Data of interest are listed in Table I. *Biliary drainage (Sept. 4, 1947)*: Bile not obtained. *Roentgen-ray studies:* Serial films of the stomach and duodenum (*Sept. 8, 1947*): negative.

Hospital course: Diagnosis: Obstructive jaundice probably caused by carcinoma of the head of the pancreas. Operation (*Sept. 13, 1947*): Total pancreatoduodenectomy. Gastrojejunostomy, choledocho-jejunostomy. *Pathologic diagnosis:* adenocarcinoma and fibrosis of the pancreas. *Postoperative course:* aside from a severe urethro-cystitis and a diarrhea, recovery rapid and complete. Discharged in good condition on *October 5, 1947* (22nd postoperative day), on a diet of carbohydrate 250 Gm., protein 120 Gm., fat 70 Gm., and with the following medication: protamine zinc insulin 10 U. b.i.d., regular insulin p.r.n., pancreatin (U.S.P.) 75.0 Gm. daily and choline chloride 1.0 Gm. daily.

Course after discharge: From *October 5, 1947* until *November 11, 1947,* patient seen once or twice weekly in the out-patient clinic. Only complaints: severe dysuria and urinary frequency. Diabetes under fairly good control with 25-30 U. of insulin. Poor home situation and patient obliged to do heavy housework soon after discharge from hospital; difficulty in maintaining weight. On *November 24, 1947,* admitted with signs and symptoms of acute intestinal obstruction of two days' duration. General condition on admission very poor. Surgery not attempted. Expired on *November 27, 1947,* eleven and a half weeks after her pancreatectomy. *Autopsy findings of importance:* Acute intestinal obstruction due to fibrous band arising from the bed of previously (1939) removed appendix; acute fibrino-purulent peritonitis; postoperative state following total pancreatoduodenectomy. Generalized arteriosclerosis. There was no evidence of any remnant or recurrence of the pancreatic carcinoma.

Case 3.—(L.T.S., Case No. 539,056). Female, aged 60 yrs. — Admitted on *January 12, 1948,* with the complaints of diarrhea and loss of 48 lbs. of weight in seven months. One month before admission onset of jaundice and appearance of diarrhea with large, greasy, light-colored stools. No pain, fever or chill. Attacks of gall bladder colic for a number of years. Known diabetic for 15 years with fairly good control on 25-30 daily U. of regular insulin. Seven months before admission B.M.R. plus 37; treated with Lugol's solution.

Physical examination: Evidence of recent weight loss. Markedly icteric. Comfortable. Temperature 98.6, pulse 90, respirations 18; blood pressure 150/80; weight 122 lbs. No exophthalmos or exophthalmic eye signs. Cardiovascular system essentially normal. Liver palpable 4 cm. below right costal margin. Gall bladder questionably palpable. The remainder of the findings unimportant.

Laboratory findings: The data of interest on blood determinations are listed in Table I. Kline exclusion serological test (*January 12, 1948*): negative. Urinalysis: positive Benedict test on repeated occasions, otherwise negative. Warm-stage stool examination and routine stool examination (*January 13, 1948*): absence of bile; undigested food elements, 4 plus guaiac. B.M.R. (*January 20, 1948*) plus 41, R.Q. 0.71; (*January 24, 1948*) plus 30. *Roentgenologic studies:* Barium enema examination of the colon (*January 16, 1948*): negative. *Cholecystograms* (*January 14, 1948*): nonfunction of the gall bladder, containing calcified gall stones. Serial films of the stomach (*January 29, 1948*): negative. *Biliary drainage* (*January 14, 1948*): no B-bile; suggestive evidence of gall stones and cholecystitis. *Duodenal drainage* (*January 14, 1948*): absence of pancreatic enzymes. *Gastric analysis* (*January 14, 1948*): fasting negative for free hydrochloric acid, all fractions containing free hydrochloric acid; chymification normal. *Electrocardiogram* (*January 31, 1948*): arteriosclerotic heart disease.

Hospital course: Diagnosis: Obstructive jaundice probably caused by carcinoma of the head of the pancreas. *Operation* (*January 31, 1948*): Total pancreatoduodenec-

TABLE III.—*Postoperative Determinations of Blood Hemoglobin, Blood Count, Blood Chemistry, Icterus Index and Liver Function.*

Case 2

TYPE OF DETERMINATION	POSTOPERATIVE DAY																POSTOP. WEEK		
	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	4	6	8
Hemoglobin, Gm. %	15.4	13.7	15.6	15.9	15.0	13.4	13.4		12.0	12.2	11.4	11.4	10.9	14.1					11.4
Erythrocytes, million/cu.mm.				4.9						4.4									
Leucocytes, thousand/cu.mm.	15.3	6.9	6.8	9.0	10.5	8.9	11.2		14.3	13.9	8.2	9.9	7.6	8.3					10.5
Sugar (fasting), mg. %	100	154	134	133	194	313	183	263	203	188	177	154	116	92	120		100	394	277
CO_2 Capacity, vol. %					67	91	93			66	57			56	58				
NPN, mg. %					43									37					
Chlorides, as NaCl, mg. %					340	373	373		420	427				477					
Albumin/Globulin, Gm. %									2.86/2.28		2.52/2.49			3.94/2.82					
Prothrombin % normal						100								95					
Total Lipids, mg. %																			590
Cholesterol, mg. %																			134
Cholesterol Esters, % total Cholesterol						67													
Icterus Index, unit				57					31		26	23	18	19	18				
Cephalin Cholesterol					+									4+					
Thymol Turbidity, unit					1									2					
Thymol Flocculation					0									0					
Hippuric Acid, oral, Gm.														0.45					
Bromsulphalein, % retention/1 hr.													13						

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tomy, splenectomy, choledochojejunostomy, gastrojejunostomy, cholecystostomy, removal of gall stones. *Pathologic diagnosis:* Adenocarcinoma of the pancreas arising in the duct system, G. 2, with metastases to the regional lymph nodes. *Postoperative course:* Rapid and complete recovery in 14 days. Discharged after some metabolic studies on *February 23, 1948.* Discharge diet: carbohydrate 250 Gm., protein 150 Gm. and fat 100 Gm. Discharge medications: Pancreatin (U.S.P.) 1.32 Gm. t.i.d.; protamine zinc insulin 5 U. A.M. and P.M. with regular insulin p.r.n.; choline chloride 1.32 Gm. t.i.d.; propylthiouracil 50 mg. t.i.d.

Course after discharge: From *February 23, to March 14* patient was seen twice weekly in the out-patient clinic. Glycosuria difficult to control, daily 2 plus to 3 plus urinary sugar but no acetone. On *March 14, 1948* patient admitted for studies (see below). On *March 26, 1948,* patient was again dismissed; returned to her home 400 miles from Detroit under care of own physician. Medication: Pancreatin 8.0 Gm. daily; protamine zinc insulin 5 U. q.a.m., regular insulin p.r.n.; propylthiouracil 50 mg. t.i.d. On *April 26, 1948,* patient reentered the hospital for follow-up studies. At this time she felt well and complained only of occasional epigastric distress after eating. Physical examination showed no noteworthy abnormality other than moderate diabetic retinopathy, O.U. Temperature, pulse and respirations were normal; blood pressure 143/78; weight 115 lbs. The laboratory findings of interest are listed in Table IV. *Serial roentgenograms* of the upper gastro-intestinal tract (*April 27, 1948*): Some obstruction at the gastro-enterostomy stoma; visualization of the biliary tract with barium; otherwise negative. (Other studies in progress.)

IMMEDIATE POSTOPERATIVE OBSERVATIONS

In addition to the physiologic disturbances that follow any extensive and lengthy operation on the upper gastro-intenstinal tract, the complete removal of the pancreas creates a special problem: that of a rapidly supervening diabetes; or if a state of diabetes already exists (as in our Cases 2 and 3), a temporary aggravation of the difficulties of controlling the diabetes.

The changes in carbohydrate metabolism and other physiologic processes were followed by daily determinations of the chemical constituents of the blood, the more important of which are listed in Tables II, III and IV and represented in Figures 2, 3 and 4. Blood sugar and CO_2 capacity often had to be determined two or more times daily because of the frequent unpredictability of their values.

During the first six to eight postoperative days the urine was collected in four daily batches and tested for glucose and acetone four times daily, each time of testing immediately preceding the next intravenous feeding. The insulin was administered in the intravenous fluid according to the results of the analysis of the urine and the blood glucose level.

The most significant and helpful data were the blood sugar, CO_2 capacity and chloride levels. In Cases 1 and 2, an alkalosis in terms of CO_2 capacity was observed: the CO_2 capacity rose as high as 94 vols. per cent. The explanation of this phenomenon is not easy to find. It has been suggested that the sudden cessation of the demand on the alkali reserve of the secretion of the highly alkaline pancreatic and duodenal juices may have set free untapped sources of alkali. In any case, the increase in CO_2 capacity had no deleterious effects and responded fairly well to treatment with medication supplying acid radicals.

TABLE IV.—*Postoperative Determinations of Blood Hemoglobin, Blood Count, Blood Chemistry, Icterus Index, Liver Function, Blood Enzymes, and Basal Metabolic Rate.*

Case 3

TYPE OF DETERMINATION	POSTOPERATIVE DAY																POSTOP. WEEK
	1	2	3	4	5	6	7	8	9	10	12	14	16	18	20	22	13
Hemoglobin, Gm. %	12.7	11.5	11.5	11.1	12.4	10.3	11.7	11.7	13.1	13.4	13.1	13.6	12.2	12.0	11.7	10.7	13.6
Leucocytes, thousand/cu.mm.	17.6	19.3	17.0	15.4	13.2	16.1	16.7	15.8	22.1	12.5	12.4	10.7	12.3	10.2	14.0	13.3	13.7
Sugar (fasting), mg. %	167	61	180	175	156	154	151	100	207	85	206	320	85	72	59	200	
CO_2 Capacity, vol. %	48	55	60		67		60	58	59	41	57	41	52	52	40	56	
NPN, mg. %										23	35	41	28		17	32	40
Chlorides, as NaCl, mg. %	463		400		420				440	460	440	320	380		514	420	460
Sodium, mg. %																	364
Phosphorus, mg. %																	4.4
Calcium, mg. %																	9.0
Potassium, mg. %																	22.5
Albumin/Globulin, Gm. %	3.84 / 1.85				3.28 / 1.74		2.82 / 1.88		3.68 / 1.64	3.00 / 2.50	2.85 / 2.17	2.63 / 2.29	2.95 / 1.85		3.82 / 2.60	2.74 / 2.04	4.64 / 1.96
Icterus Index, unit	45	39	45		32	31	26	27	26	15	18	16	20		16	12	
Prothrombin, % normal													72				
Total Lipids, mg. %	1020				838				645	562		532	533	570	613		593
Cholesterol, mg. %	450				410		427		178	286	194	208	235		164	200	210
Cholesterol Esters, % total															52	40	43
Bromsulphalein, % retention in 1 hour																	13
Alk. Phosphatase, unit																	9.2
Hippuric Acid, oral, Gm.																	2.51
BMR, % above normal																	52
Lipase, unit	1.07		1.00		0.6				0.7	0.75		0.4	0.37			0.5	1.25
Amylase, unit	37		44		73		41		56	15			13		18	29	0

The blood chloride level was a valuable guide for the estimation of intravenous feedings. As one would expect, it showed no significant fluctuations as long as the intravenous therapy was adequate.

The behavior of the blood glucose values will be discussed below, as will also be that of the icterus index, blood lipids and blood lipase and amylase. The remaining blood chemical studies showed no characteristic alterations.

CARBOHYDRATE METABOLISM AFTER TOTAL PANCREATECTOMY

Immediate postoperative period.—As observed in our patients, two striking facts stand out in the immediate postoperative course of total surgical diabetes. First, the insulin requirement for maintaining a blood glucose level near the normal range is surprisingly low in comparison with the requirements of diabetes mellitus in which almost always a considerable amount of functioning island tissue is still present. As a corollary to this fact, the sensitivity to insulin of the depancreatized patient is much greater than that of the patient with diabetes mellitus. Our patients were satisfactorily controlled with from 10 to 60 units of insulin daily, the average number of daily units needed lying just around 30. On the other hand, we observed a severe insulin shock following the administration of 10 units of insulin three hours after a blood glucose level of 430 mg. per 100 cc. The second outstanding fact is the capricious behavior of the blood sugar. An effort was made to administer the intravenous fluids containing glucose at regular intervals in close correlation with the blood chemistry determinations and urine tests. It was not possible, however, to arrive at an entirely reliable scheme that would keep the urine persistently sugar-free yet not lower the blood sugar to a dangerous level. Some tentative explanations for this phenomenon will be offered presently.

Because of the insulin sensitivity and of the variability of the hyperglycemia of the depancreatized patient, we have endeavored to regulate the blood sugar level in the immediate postoperative period with the aim of keeping it well above rather than very near the normal range, that is, around 200 mg. per 100 cc. Either theoretically or as judged by practical experience, at least as a short-term type of management, this method has shown no untoward effects and has proved safe.

Later postoperative period.—The immediate postoperative period can be regarded as closed when the patient is well established on a satisfactory maintenance diet. In our cases this period extended from 14 to 23 days.

A rather trying space of time begins when the depancreatized patient starts taking food by mouth. Because of the inconstant appetite and poor digestion and absorption, the amount of actual food intake is hard to reckon and the control of the diabetes usually slips (cf. Fig. 1, 2 and 3).

After the patient has become well accustomed to his diet, a satisfactory control is not too difficult to attain. Given constant circumstances of dietary

intake, activity and health, the insulin requirement of the depancreatized patient does not vary widely. Case 1 lived a life of moderate activity in comfort for six months under good control of his diabetes with 26-28 units of protamine zinc insulin taken in the morning. Later his dosage rose to 40 units daily and toward the end of his life his control became difficult to maintain.

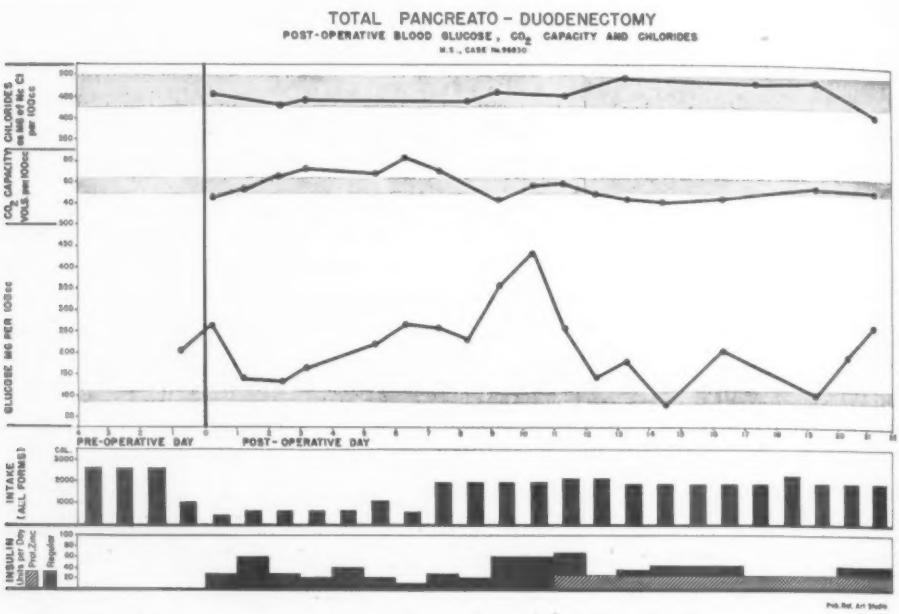

FIG. 1.—Case 1.—Postoperative changes in blood chlorides, CO_2 capacity and sugar. (Determinations on fasting blood specimens. Shaded bands for normal ranges of values.) — The figures for the total daily caloric intake represent calculated values. The average daily composition of the diet from which the caloric values were derived was fairly uniform for each of the following periods:—Last three preoperative days: carbohydrate, 350 Gm.; protein, 200 Gm.; fat, 50 Gm. First to sixth postoperative days: carbohydrate, 150 Gm.; protein, 35 Gm. Seventh to twenty-first postoperative days: carbohydrate, 200 Gm.; protein, 120 Gm.; fat, 50 Gm.

Changes in diet, bowel habits (diarrhea), and general health upset the control of these patients seemingly more readily than that of patients with diabetes mellitus. Case 2 was controlled in a satisfactory manner only for short periods of time on account of a recurrent urethro-cystitis of moderate severity. When in good health, her daily need was about 30 units; during the spells of illness this went up to 40 or 45 units. Control of the diabetes in Case 3 has been an especially difficult problem owing to the high basal metabolic rate (see below). Her daily requirement has been around 40 units. On this she feels well and maintains her weight but spills 2 to 3 plus sugar in her urine almost daily. A closer control in her case is dangerous since she has developed severe hypoglycemic shock (blood sugar 43 mg. per 100

cc.) upon the subcutaneous administration (by mistake) of 10 units of insulin four hours after a meal containing about 120 Gm. of glucose equivalent. The sensitivity to insulin, seen in an increased degree in this case, was not conspicuous in Case 1, but was quite evident in Case 2. This propensity made the use of protamine zinc insulin a matter of some risk in Case 3 and to a less extent in Case 2 also. Ten units of protamine

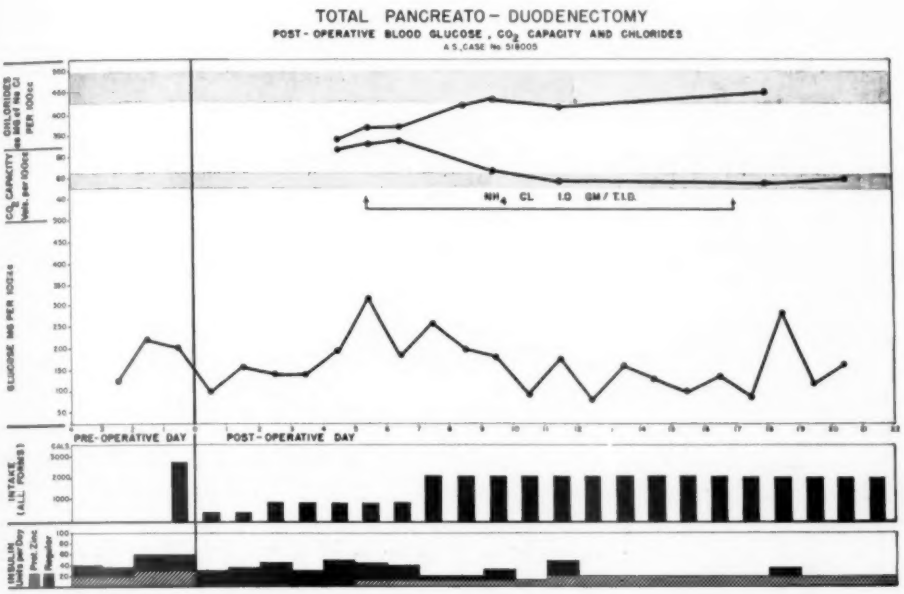

FIG. 2.—Case 2—Postoperative changes in blood chlorides, CO_2 capacity and sugar. (Determinations on fasting blood specimens. Shaded bands for normal ranges of values.) — The figures for the total daily caloric intake represent calculated values. The average daily composition of the diet from which the caloric values were derived was fairly uniform for each of the following periods. Preoperatively: carbohydrate, 350 Gm.; protein, 120 Gm.; fat, 70 Gm. First to sixth postoperative days: carbohydrate, 150 Gm.; protein, 125 Gm. Seventh to twenty-first postoperative days: carbohydrate, 250 Gm.; protein, 110 Gm.; fat, 80 Gm.

zinc insulin taken at 8 A.M. and 6 P.M. would on occasion cause a mild hypoglycemic reaction in the following morning, before the next injection, apparently by virtue of the summation of the effect of the two injections of the previous day. Case 3 became, for this reason, very antagonistic to the use of the long-lasting preparation. Nevertheless, whenever possible we attempt to administer about ½ to ⅔ of the daily insulin requirement in the form of protamine zinc insulin.

Because of the insulin sensitivity, we prefer to regulate the insulin dosage, also in the later postoperative period, in such a manner as to insure a fasting blood sugar on the hyperglycemic side (150 plus mg.).

The relatively low insulin requirement in total surgical diabetes has given occasion for much speculation. The basal insulin requirement of a totally depancreatized 60 kg. man has been estimated on the basis of calculations from animal experiments as 1.014 unit per hour or about 24 units per day.[13] If one increases this figure by 50 per cent to allow for the needs of the metabolic state for average activity the estimate of 36 units obtained is amazingly close to the average actually observed in our cases. From evidence such as this it has been suggested that in diabetes mellitus

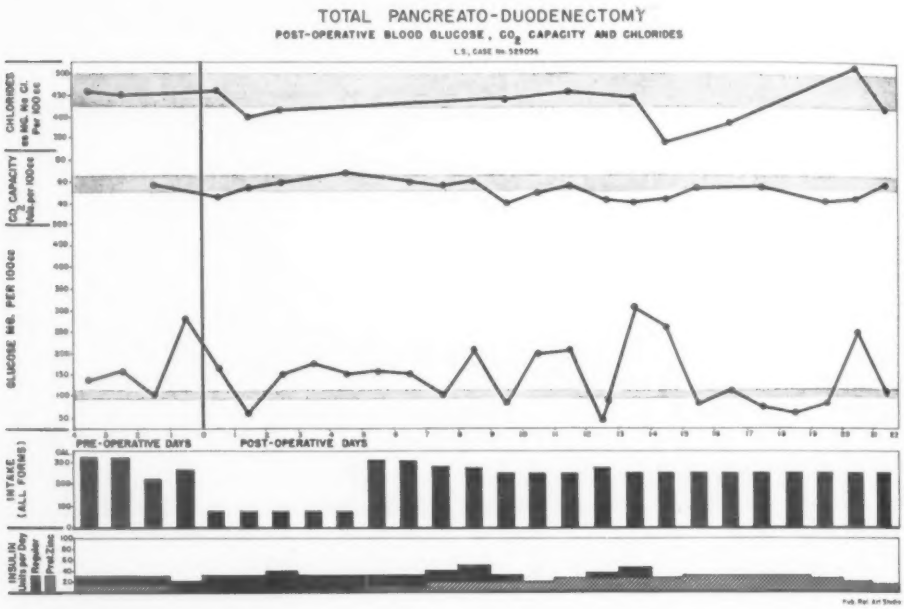

FIG. 3.—Case 3.—Postoperative changes in blood chlorides, CO_2 capacity and sugar. (Determinations on fasting blood specimens. Shaded bands for normal ranges of values.) — The figures for the total daily caloric intake represent calculated values. The average daily composition of the diet from which the caloric values were derived was fairly uniform for each of the following periods: Preoperatively: carbohydrate, 350 Gm.; protein 100 Gm.; fat, 60 Gm. First to four postoperative days: carbohydrate, 150 Gm.; protein, 50 Gm. Fifth to twenty-first postoperative days: carbohydrate, 250 Gm.; protein, 150 Gm.; fat, 100 Gm.

there is a factor at work that is absent in pure surgical diabetes. The recent work on the role of the pituitary and adrenal glands in the regulation of carbohydrate metabolism seems to favor such an assumption. In a recent laboratory experiment [14] the sequence of events observed in diabetic patients that underwent total pancreatectomy (Cases 2 and 3) has been duplicated to some extent. After diabetes of a determined severity had been produced in dogs by the administration of alloxan, total pancreatectomy decreased the degree of insulin requirement. The authors postulate

that there is a second pancreatic hormone generally antagonistic to insulin. It is possible that further observations on patients rendered diabetic surgically will shed light on these complex problems.

The seeming contradiction of the simultaneous presence of insulin sensitivity and tendency for hyperglycemia, and in particular the frequent un-

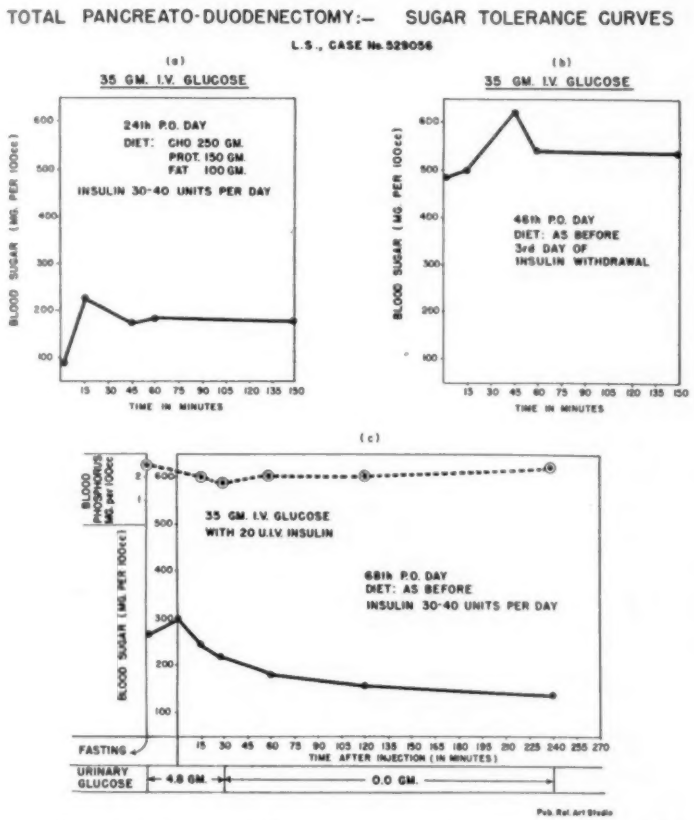

FIG. 4.—Glucose tolerance curves at various postoperative periods without [(a) and (b)] and with [(c)] simultaneous administration of insulin. (Case 3.)—(Note: The time coordinate for curve (c) is modified in order to permit the representation of an additional blood glucose determination made directly on the completion of the intravenus injection; on the abscissa this value, rather than the fasting value, is placed in the zero position.)

predictability of the blood glucose level are understandable in the terms of the physiologic activity of insulin. Figure 4 presents three characteristic sugar tolerance curves in Case 3. It can be seen from curves (a) and (b) that the glucose introduced into the blood stream is utilized at a very slow rate. Evidently there is no mechanism upon which the high blood sugar

level would exert an influence to speed up utilization by glycogenesis and oxidation. In curve (c) the presence of the insulin assures an initial utilization of the glucose, but once the insulin is expended the curve flattens out. Thus, the lack of a steady supply of insulin, gauged to the constantly changing needs of the organism seriously impairs the deposition of glycogen in the liver and its oxidation in the tissues. The periodic injection of insulin repairs this defect only in part: adequate glycogenesis and oxidation goes on only periodically, while the insulin is present. At other times, sugar may be piled up in the blood, or, because of the depleted liver glycogen, the blood sugar may be inadequate to respond to the sudden appearance of insulin in the blood stream.

The renal threshold for blood sugar may become elevated in depancreatized patients. In Case 2 blood sugar levels of 200 to 250 mg. per cent would be present without glycosuria; the threshold of this patient was variable and it seemed to be higher after periods of inadequate control. The renal threshold for glucose of Case 3 has been around 200 mg. per cent quite consistently during the past two months.

Hyperthyroidism aggravates the problem of controlling the diabetes of the patient without a pancreas. As has already been mentioned, Case 3 illustrates this point. This patient has had a basal metabolic rate varying from plus 30 to plus 59 at least for the past ten months. For the past four months her rate has been kept at around plus 30 by the administration of 150 mg. of propylthiouracil daily. Until now no effort has been made to reduce the basal metabolic rate below this level for the following reasons: Before her operation (January 31, 1948) a varying schedule of dosages with Lugol's solution and propylthiouracil was tested. She seemed to be refractory to Lugol's solution. Propylthiouracil 50 mg. t.i.d. caused a remission of her rate from plus 42 to plus 30. Since she had no other evidence of hyperthyroidism than the elevated metabolic rate (in particular, no cardiac involvement, no eye signs, no nervous system manifestations) and since she had obstructive jaundice of increasing severity, it was thought the lesser risk to operate on her rather than to wait until her metabolic rate had been further reduced. She stood the operative procedure very well and in the immediate postoperative period, upon the whole, her high metabolic rate was found to be an advantage rather than a hindrance. Since certain investigations had been started and some others planned, and since under the circumstances the high metabolic rate was causing no harm, it was decided to maintain the rate at plus 30 until the completion of the study, at the end of which an attempt will be made to lower it by increasing the dosage of propylthiouracil, or, if this should fail, by surgical means.

STUDIES ON INSULIN WITHDRAWAL

Several facts urged an inquiry into the behavior of the depancreatized patient after insulin withdrawal. There were observations made during the

immediate postoperative period that suggested that the depancreatized patient did not form ketone bodies as readily as one would have expected. It seemed possible that observations during a period of insulin deprivation might reveal characteristics in the course of events that might demarcate surgical diabetes from diabetes mellitus. It also seemed a practical necessity

TABLE V.—*Determinations of Blood Hemoglobin and Count, Blood Chemistry, Liver Function, Basal Metabolic Rate, Urine Chemistry, and Body Weight Before, During and After Insulin Withdrawal.*

Case 3

Type of Determination	DAY OF OBSERVATION								
	1	2	3	4	5	6	7	8	9
BMR, % above normal	29	30	34	38	46	59	46	41	39
Respiratory Quotient	.72	.73	.70	.69	.68	.67	.66	.69	.71
Urine acetone Gm./24 hr.	0.005	0.096	0.009	0.477	1.903	3.490	0.579	0.025	
Urine β-hydroxybutyric acid/24 hr.	0.018	0.126	0.071	0.397	3.771	7.570	0.313	0.056	
Urine sugar, Gm./24 hr.	40.2	64.3	45.3	180.0	200.0	168.7	116.5	80.0	
Urine nitrogen Gm./72 hr.		34.79			41.51			44.72	
Urine chlorides (as NaCl.) Gm.24/hr.				15.1	11.9	5.0	5.6	4.2	
Weight, lbs.	111		109	110½		108¼	109½	110¼	
Hemoglobin, Gm. %	11.5	12.4	12.5			12.2	12.0	12.9	11.8
Erythrocytes, million/cu. mm.	3.76	4.09				3.60		4.20	3.57
Leucocytes, thousand/cu. mm.		11.6	13.5			14.0	17.1	11.4	13.1
Sugar (fasting) mg. %	204		136	294	313	480	156	380	297
CO_2 Capacity, vol. %	46	55	54	54	54	43	56	66	50
NPN, mg. %					39				
Urea N, mg. %	18.0			18.0	19.0	21.9		21.0	
Chlorides, as NaCl, mg. %	427	413	407	393	433	427	413	407	420
Sodium, mg. %	317	246	310	301	260	293	276	290	296
Potassium, mg. %	24	19	28	21		20	28	21	
Albumin/Globulin, Gm. %	3.29		2.42	3.17	3.12	3.02		3.36	3.68
	3.04		4.12	2.50	2.60	2.50		2.27	1.74
Acetone, mg. %	1.9	2.0	3.3	3.7	11.7	10.8	4.7	4.0	2.4
Total Lipids, mg. %	915		865	685	714	892		756	
Cholesterol, mg. %	279		259	164	300	228	183	185	152
Cholesterol Esters, % total	53%		49%						
Icterus index, unit	15								
Bilirubin, direct, mg. %	0.13								
Bilirubin, total, mg. %	0.39								
Cephalin cholesterol	4+				4+				
Thymol turbidity, unit	10				5				
Thymol flocculation	Neg.				Neg.				
Bromsulphalein % ret./hr.	12								
Hippuric acid, oral, Gm.	2.51								
Lipase, unit	1.2			0.3			1.5		

to have some knowledge of the margin of safety that these patients possess between persistent hyperglycemia and diabetic acidosis, especially since our preference is for treatment on the hyperglycemic side. This last consideration has a special importance in view of the observation that depancreatized dogs, once they develop diabetic acidosis, are difficult to bring under control

again. For all these reasons, the following experiment was carried out in Case 3, starting on the 44th postoperative day.

After a period of adjustment of 48 hours on a diet consisting of 250 Gm. of carbohydrates, 150 Gm. of protein and 100 Gm. of fat, daily stool and urine specimens were collected for nine days (from the 46th to the 54th postoperative day). During this time the stool was quantitatively analyzed for total nitrogen, fat, fatty acids and calcium, and the urine for total nitrogen, glucose, acetone, β-hydroxybutyric acid and chlorides. The nine-day period of observation can be grouped in three three-day subdivisions. During the first three-day period insulin was administered in the usual amounts to maintain a satisfactory control of the diabetes. During the next three-day period insulin was discontinued. During the last three-day period insulin was again administered to re-establish diabetic control. Throughout the experiment patient was allowed to be up and around in her room. Daily determinations of numerous blood chemical constituents and of the basal metabolic rate were made; during the 4th, 5th and 6th days of observation blood sugar, blood CO_2 capacity and blood acetone bodies were measured three times daily, at 7:30 A.M., 4:30 P.M. and 2:00 A.M. The results of these studies are shown in Tables V and VIII and in Figures 5 and 6.

In evaluating the significance of these findings, it must be pointed out that the control of our patient's diabetes at the beginning of the experiment was not as good as we should have liked to have it. During the preliminary period she spilled 40.2 to 64.3 Gm. of glucose and 18 to 126 mg. of β-hydroxybutyric acid daily. It was impossible, however, to prolong this preliminary phase since patient had come from a long distance for a strictly defined length of hospitalization and she was unwilling to change the arrangement previously agreed upon.

The clinical effects of insulin deprivation were unexpectedly innocuous. During the last 24 hours of the withdrawal of insulin the patient felt extremely weak and moderately drowsy, but otherwise was entirely comfortable. Her appetite was good during the first two days and only slightly impaired during the last day; her calculated caloric intake during the three days, respectively, were as follows: 2246, 2542 and 2334 Calories. Aside from an acetone odor of her breath she showed none of the usual clinical signs of diabetic acidosis.

Upon the whole the chemical changes likewise show a degree of acidosis that is less marked than one would expect from comparison with clinical diabetes. The daily amount of urinary acetone excreted on the last day of experiment reached the value of 3.49 Gm.; the amount of β-hydroxybutyric acid excreted during the same time was 7.57 Gm.* The highest blood acetone level was 12.9 mg. per cent. In severe diabetes daily urinary acetone

* Expressed as acetone.

bodies have been reported in the range of 6.0 Gm. for acetone and 100.0 Gm. for β-hydroxybutyric acid.[15] Thus, the degree of acidosis of this patient after three days of complete deprivation of insulin could be classified as moderately severe in terms of clinical diabetes. The significance of this

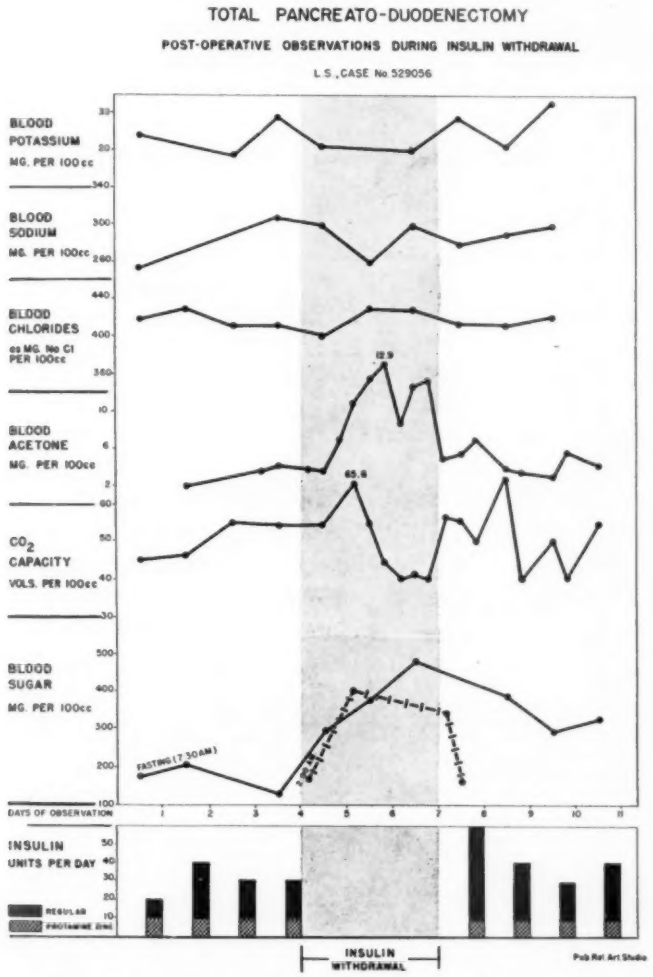

FIG. 5.—Blood postasium, sodium, chlorides, acetone, CO_2 capacity and sugar levels before, during and after insulin withdrawal; daily insulin requirement. (Unless otherwise marked, values are fasting.) (Case 3.)

fact is probably enhanced by the presence of a high metabolic rate in the patient.

The basal metabolic rate during the period of ketosis rose from an initial plus 34 to plus 59. The respiratory quotient declined from .73 to .66 The patient lost two pounds of weight during the experiment.

The levels of blood potassium and sodium showed no significant change. The other chemical constituents of the blood likewise remained within normal limits. The temporary increase in the urinary chloride excretion very likely was the result of diuresis.

The relative mildness of the acidosis was further attested by its relatively swift disappearance on treatment. At the completion of 72 hours of insulin deprivation a urethral catheter was inserted and urine from the bladder was tested every two hours. For Benedict reactions over 2 plus, 20 units of

TABLE VI.—*Preoperative Nitrogen Balance*

Case 3

Calculated diet: Carbohydrate 300 Gm., protein 90 Gm., fat 93 Gm.
Medication: none

Period of Study Days	Urine N Gm.	Stool N Gm.	Total Output N Gm.	Total Intake N Gm.	N Balance Gm.
6	49.81	38.78	88.59	86.16	—2.43

Daily averages: urinary N, 6.46 Gm.; fecal N, 6.30 Gm.

regular insulin were administered hypodermically as an initial dose and 10 units thereafter. No other treatment was given. After the injection of 60 units of insulin in the course of ten hours, the Benedict reaction showed only a trace of glucose, and there was only a trace of acetone in the urine. The fasting blood sugar at this time was 151 mg. per cent. The patient continued to have a moderate glycosuria for the subsequent 48 hours of observation, but the blood and urinary acetone remained near normal levels.

Six hours after the beginning of the resumption of insulin the patient's drowsiness had cleared. She gradually became more active and in 24 hours she was going about her business as usual. She insisted on leaving the hospital on schedule, 72 hours after the termination of the period of insulin withdrawal. (For this reason her diabetic control could not be completely re-established.)

Concurrently with the investigation of the effects of insulin withdrawal, nitrogen balance studies were carried out. The patient was offered a diet calculated to consist of 250 Gm. of carbohydrates, 150 Gm. of protein and 100 Gm. of fat. She took the diet well, her intake varying from 2246 to 2672 Cals. during the nine days. Collection of the specimens was for three-day intervals. The nitrogen content of the actual intake was determined by analysis. The carbohydrate and fat contents of the ingested food were not measured analytically. The patient continued to be given her previous medications (pancreatin (U.S.P.) 4.0 Gm., choline chloride 4.0 Gm., propylthiouracil 0.150 Gm. daily).

Table VIII shows the results of this study. The significant change noted was the increase in both the daily urinary and the daily fecal nitrogen excretion. Whereas during a previous nitrogen balance study, during which

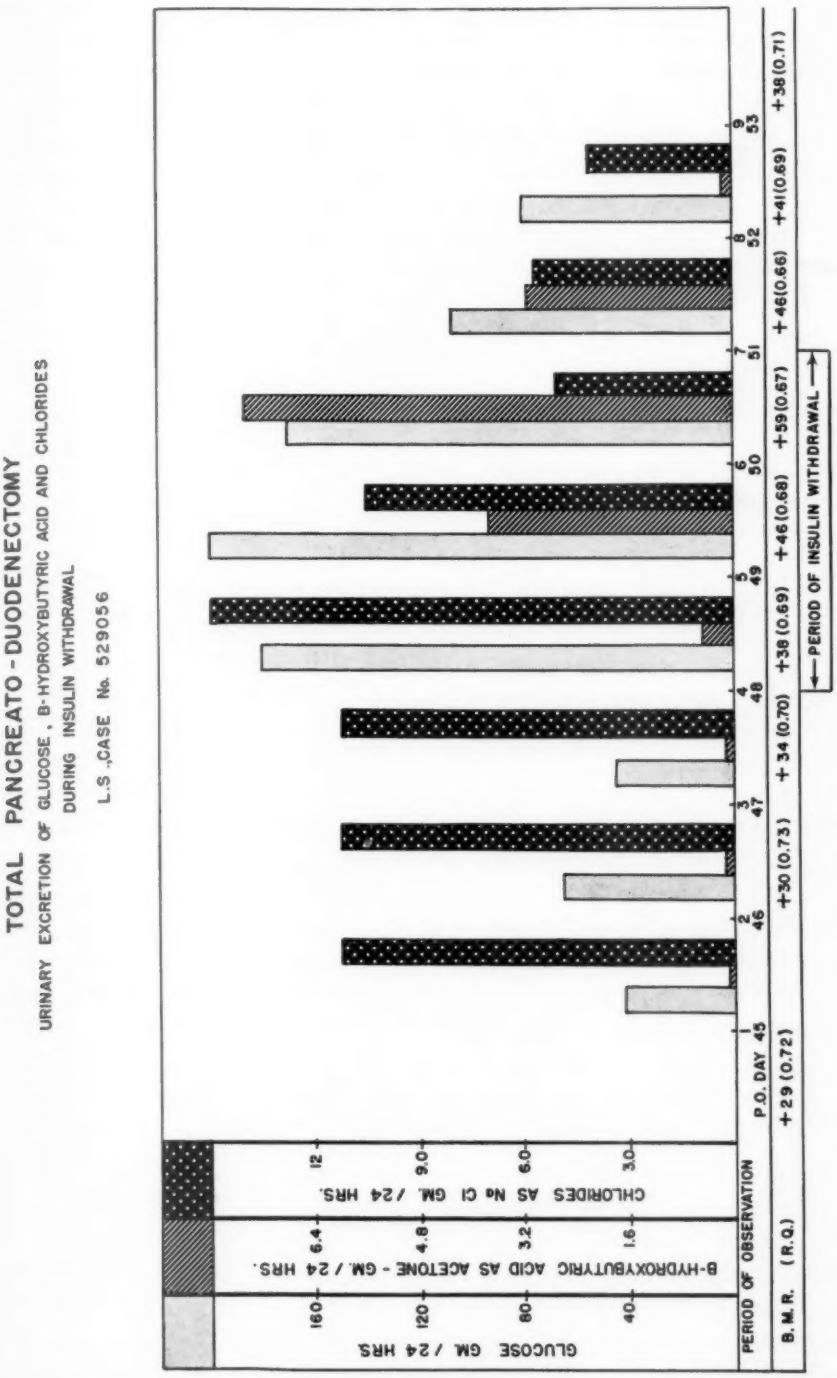

FIG. 6.—Urinary excretion of glucose, β-hydroxybutyric acid and chlorides during insulin withdrawal. Changes in the basal metabolic rate and in the respiratory quotient. (Case 3.)

patient received the same medications including pancreatin, the daily average urinary nitrogen was 6.79 Gm. and the daily average fecal nitrogen was 2.21 Gm. (Table VII), these values rose to 13.44 Gm. and 4.38 Gm., respectively, during the period that includes the three days of insulin withdrawal as well as the three days preceding it and the three days following it. There was an average daily nitrogen deficit of 5.77 Gm. Unfortunately, the intake of nitrogen was not determined daily, but was for the total period of nine days. Thus, it is not possible to tell precisely the magnitude of nitrogen deficit for the three days of insulin deprivation as compared to the other two periods. Since, however, the fecal nitrogen loss was very

TABLE VII.—*Postoperative Nitrogen Balance.*

Case 3

Calculated diet: Carbohydrate 250 Gm., protein 150 Gm., fat 100 Gm.,
Medication: Pancreatin (U.S.P.) 4.0 Gm./day.

Period of Study * Days	Urine N Gm.	Stool N Gm.	Total Output N Gm.	Total Intake N Gm.	N Balance
5	33.96	11.04	45.00	69.21	24.21

Daily averages: Urinary N, 6.79 Gm.; fecal N, 2.21 Gm.
* Nineteenth to twenty-third postoperative days.

constant from period to period, it is possible to refer to the urinary nitrogen as an index of the deficit per period. The urinary nitrogen in the three periods was 34.79, 41.51 and 44.72 Gm., respectively. Thus the urinary nitrogen loss in the second period was 19.3 per cent and in the third period 28.5 per cent above that in the first period. The increase in the loss of urinary nitrogen may probably be ascribed to the effects of ketosis, largely resulting from the stepped up protein catabolism. The diuresis (up to 4500 cc. a day) during the second and third periods was very likely another factor. It is not easy to explain the increase in fecal nitrogen. One might suppose that the pancreatin dosage, which was small but had previously proved adequate, apparently became insufficient during the altered metabolic demands of the period of observation. Strangely, however, the efficiency of fat digestion showed no important deterioration during this time (Table IX).

No significant change was found in the urinary and fecal calcium excretion during the same period of observation.

THE EFFECTS OF THE ABSENCE OF EXTERNAL PANCREATIC SECRETIONS SUBSTITUTION THERAPY

Observations on Fecal Nitrogen and Fat.—Studies of fat and protein digestion were made in Case 3. A few scattered observations of some interest were gathered in Cases 1 and 2.

In case 1 there was no quantitative determination of the stool fat and nitrogen content before operation. On the eighth postoperative day, patient

TABLE VIII.—*Postoperative Nitrogen and Calcium Balance Partly During Insulin Withdrawal*
Case 3

Calculated Diet: Carbohydrate 250 Gm., protein, 150 Gm., fat 100 Gm. — *Medication:* Pancreatin (U.S.P.) 4.0 Gm./day.

Period of Study (P. O. Day)	Urine N Gm.	Stool N Gm.	Total N Output Gm.	Total N Intake Gm.	N Balance Gm.	Urine Ca Gm.	Stool Ca Gm.	Total Ca Output Gm.	Total Ca Intake Gm.	Ca Balance Gm.
46th-48th	34.79	13.75	48.54			1.084	3.109	4.193		
49th-51st*	41.51	13.14	54.65			1.346	1.216	2.562		
52nd-54th	44.72	12.55	57.27			0.994	4.651	5.645		
			160.46	108.52	—51.94			12.400	12.078	—0.322

Daily average values: Urinary N, 13.44 Gm.; fecal N, 4.38 Gm.; N deficit, 5.77 Gm. — Urinary Ca, 0.380 Gm.; fecal Ca, 0.997 Gm.; Ca deficit, 0.036 Gm.

*Insulin withdrawn on the 49th to 51st postoperative days.

was placed on pancreatin (U.S.P.) in the dosage of 3.0 Gm. daily. He complained of gastric distress following the ingestion of this drug and often omitted it. During the third postoperative month he had completely stopped taking the medication. On a prescribed diet of carbohydrates 200 Gm., protein 120 Gm. and fat 60 Gm., on the 100th and 101st postoperative days the average daily fecal nitrogen was 0.8 Gm. and the amount of total fats in the stool was 38.7 per cent of the dry weight (normal average being 17.5 per cent[16, 17]). Patient had no serious disturbance of bowel movements. During the 10th postoperative month, after several days of regular pancreatin intake in the dosage mentioned, and on a diet of carbohydrate 300 Gm., protein 135 Gm., fat 100 Gm., on three alternate days the percentage by dry weight of the total stool fat was as follows: 25.6, 15.3 and 21.9.

Preoperative quantitative data on the stool fat and nitrogen are lacking also in Case 2. On the 20th, 21st and 22nd postoperative days the stool was collected and analyzed quantitatively for nitrogen and fat; the nitrogen content of the urine excreted during this time was also determined; the prescribed diet contained 250 Gm. of carbohydrate, 120 Gm. of protein, and 70 Gm. of fat. At this time patient was receiving 75 Gm. of pancreatin (U.S.P.) daily. The amount of total fat in the stool on the three days was 28, 19 and 22.4 per cent of dry weight respectively; the average daily fecal nitrogen was 0.93 Gm. and the daily urinary nitrogen 6.05 Gm.

The meaning of such random data is doubtful. The nitrogen determinations on the stool and urine without a knowledge of the true intake and after such short collections must be disregarded. Some remarks should be made, however, in connection with the values for stool fat. In Case 1 it is surprising to find a stool fat content very near the normal range on an ingestion of pancreatin as low as the

equivalent of 3.0 Gm. of U.S.P. pancreatin. It is also noteworthy that the same patient had no serious diarrhea when his stool contained 38.7 per cent of fat by dry weight. The very large does of pancreatin was prescribed in Case 2 in an attempt to control patient's annoying frequency of bowel movements, the rather hasty assumption having been made that this was due to incomplete digestion of the dietary fat. Quantitative analysis of the stool disclosed that total fats were in the upper range of normal values. Eventually the dosage of pancreatin was reduced and the diarrhea controlled by conventional means of treatment. This observation, namely that frequent loose stools after total pancreatectomy may be due to causes unrelated to the absence of pancreatic enzymes, was made also in Case 3.

TABLE IX.—*Postoperative Fat Content of Stool*

Case 3

Calculated Diet: Carbohydrate 250 Gm.; protein 150 Gm.; fat 100 Gm.—*Medication:* Pancreatin (U.S.P.) 4.0 Gm./day

P.O. Day	Wet Wt. of Stool Gm.	Wt. of Stool Fat Gm.	Fat Gm. per 100 Gm. Dry Stool	Wt. of Fatty Acids Gm.	Fatty Acids Gm. per 100 Gm. Fat
46	380	39.4	34.8	31.9	81
47	521	43.7	30.5	35.9	82
48	196	19.2	32.6	15.7	81
50	472	14.0	11.6	9.5	67
52	504	15.7	12.2	10.0	64
53	284	11.5	12.5	7.6	66
54	349	15.0	13.5	9.4	63

Average daily fecal fat: 22.6 Gm. (21 per cent of dry wt.)
Average daily fecal fatty acids: 17.1 Gm. (75.7 per cent of fat)

Remark: Average *preoperative* fat content of stool on a diet containing about 90 Gm. of fat, and without medication (48 hr. collection): 52.3 per cent of dry wt. of feces.

(In neither case, however, did the stool have the characteristics of steatorrhea.)

It should be pointed out that the pancreatin preparations used in the above cases, as well as in the studies to be described, were not uniform. All dosages are expressed in terms of U. S. P. pancreatin, the claims of potency by the manufacturer being used as basis for transcribing the values.

More systematic investigations regarding protein and fat digestion and absorption were carried out in Case 3.

Ten days before the date of operation, a six-day nitrogen balance study was begun. In this as in the following studies the collections of stool and urine as well as the samples and refused portions of the diet were pooled for three-day (rarely, two-day) periods. The beginning and end of each period was designated by charcoal and carmine markers. The calculated diet contained 300 Gm. of carbohydrate, 90 Gm. of protein and 93 Gm. of fat daily. No medication was given. The results of this study are shown in Table VI. The average daily fecal nitrogen was high, representing 39.4 per cent of the daily nitrogen intake. As shown by enzyme studies of the duodenal contents this patient had a complete obstruction of the main pancreatic duct preoperatively. The insufficiency of protein digestion

was, therefore, to be expected. Determination of the fat content of the stool after a 48 hour collection, 14 days before operation showed a total fat value of 52.3 per cent of dry weight on a diet containing about 90 Gm. of fat. Thus, the fat digestion was similarly impaired. (As will be recalled, one of patient's important preoperative complaints was a severe persistent diarrhea consisting of bulky, soft or liquid stools.)

Patient began taking food by mouth on the fourth postoperative day. After a trial with several brands and dosage schemes of pancreatin, the preparation "panteric granules" (Parke, Davis and Co.) was selected in a dosage equivalent to 4.0 Gm. of U. S. P. pancreatin daily. This amount was selected empirically. It was well tolerated and although it appeared very small, during its early administration patient's stools were of normal appearance and size.

On the 19th to 23rd postoperative days a five-day nitrogen balance study was undertaken in order to ascertain whether the dosage of pancreatin administered was in fact adequate. The data obtained are listed in Table VII. It is evident that patient was in positive nitrogen balance and that the daily stool nitrogen was not above the normal average. Patient was discharged on the same diet and same dosage of pancreatin on the 25th postoperative day.

She was readmitted on the 44th postoperative day for further investigations. In conjunction with studies on carbohydrate metabolism, nitrogen balance studies were also carried out. The results and the significance of the data so obtained have already been dealt with. Some further comment may be made on the study of the loss of fecal fat during this period, referred to in the same paragraph (Table IX). This was not a true balance study since the intake of fat was not quantitatively determined. The trend of the findings is definite enough and the number of determinations sufficiently large, however, to permit the conclusion that fat digestion at this time was essentially normal. The behavior of fecal calcium, showing no excessive loss, would also confirm this. The high percentage of fatty acids in the lipid mixture may be interpreted as another evidence of efficient fat-splitting in the intestinal tract. (However, the significance of the neutral fat/fatty acid ratio has been questioned.) Nevertheless, in order to avoid any possibility of underdosage at the end of the experiment the amount of pancreatin given was raised to 8.0 Gms. daily (2.0 Gm. with each one of four meals); patient was dismissed on this dosage, with her diet as before.

On this regimen and medication she gained eight pounds in four weeks after her return home; she has remained free from diarrhea, and has been in excellent general health.

Our studies have not determined the optimum dosage of substitution therapy for the total lack of pancreatic enzymes. They suggest, however, that the large doses of pancreatin that are at times recommended[18] are prob-

ably unnecessary. They further seem to show that the appearance of diarrhea in the absence of pancreatic enzymes is dependent on the amount of undigested fat rather than on the loss of nitrogenous substances in the stool. Moreover, an increased loss of nitrogen in the stool may seemingly take place in the presence of relatively normal fat digestion.

POSTOPERATIVE AMYLASE AND LIPASE CONTENT OF BLOOD

It was an interesting finding that, as judged by the conventional methods of determination, lipase and amylase do not completely disappear from the blood stream for many weeks after total pancreatectomy. Amylase

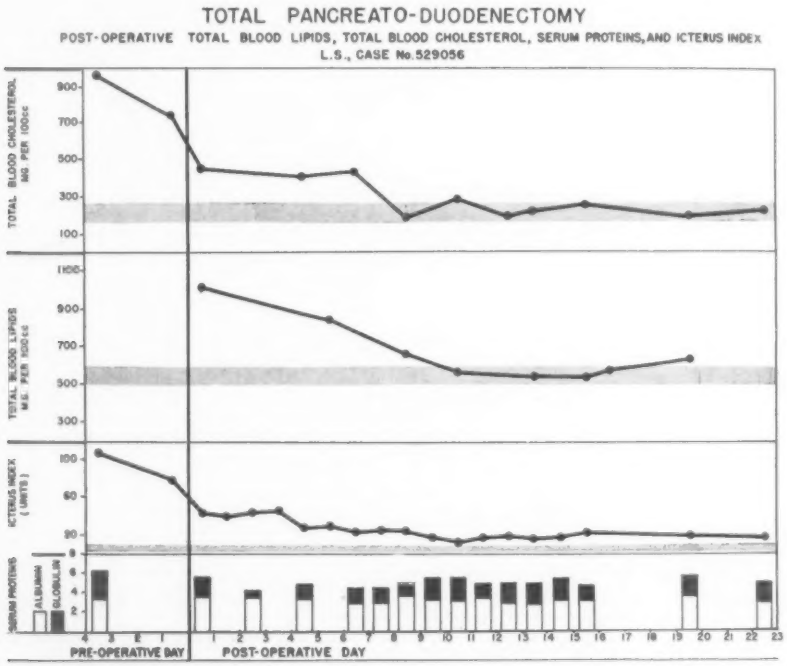

FIG. 7.—Changes in blood lipids and icterus index in a case of normal postoperative recovery. (Case 3.)

was detectable forty weeks postoperatively in case 1 (Table II). Examination in the 13th postoperative week revealed the presence of blood lipase in Case 3.

LIPID METABOLISM

THE QUESTION OF LIPOTROPIC FACTOR

In order to prevent changes in the liver that, on the analogy of animal experiments,[19] were expected to take place in the depancreatized human, the administration of choline chloride was begun soon after operation in daily doses of 3 to 4 Gms. in Cases 2 and 3. Case 1 reecived no choline chloride or other lipotropic substance. For the last month of observation the drug

was also discontinued in Case 3. When the liver was examined at autopsy in Case 1 after 14 months of survival, it was found to show no evidence of parenchymal change. Liver function tests before death likewise failed to show impairment (Table II). In Case 3 liver function tests, in particular the bromosulphophthalein test, revealed no deterioration during the short period of deprivation of choline (Table IV).

Both these patients received pancreatin daily (Case 1 only intermittently), and pancreatin contains choline. The daily preventive dose of choline, however, is calculated as 4-5 Gm., and the choline content of the pancreatin used was only 8.28 mg./Gm.[20] Thus pancreatin could not have served as a source of the allegedly needed choline.

From the findings in the two cases mentioned it appears that a lipotropic pancreatic substance either is unnecessary for lipid metabolism in the human, or, if it is required, it is supplied in the average diet in sufficient quantity. It seems superfluous to provide the lipotropic factor in the form of medication.

With reference to lipid metabolism in the depancreatized patient, the *trends in blood lipid levels* may also be briefly mentioned. Unfortunately the amount of total blood lipids was not preoperatively determined in any of the cases. In *Case 1* postoperative total lipids and cholesterol were measured rather frequently. (Table II shows some of the values.) During the first three postoperative weeks the amount of total lipids ranged between a low of 563 mg. per cent and a high of 709 mg. per cent; no cholesteral determinations were made during this time. During the fifteenth postoperative week the ranges of total blood fats and total cholesterol were as follows: lipids, 528-525 mg. per cent, total cholesterol, 107-128 mg. per cent; during the fortieth postoperative week the total lipids were 390 mg. There were no further determinations. In *Case 2* we have only the following values: Preoperative total cholesterol, 276 mg. per cent; eighth postoperative week, total lipids, 390 mg. per cent; twelfth postoperative week, total lipids, 420 mg. per cent. In *Case 3* the levels were as follows: preoperative total cholesterol 980 and 946 mg. per cent (10 per cent being ester); during the first three postoperative weeks the total cholesterol steadily decreased from 450 to 200 mg. per cent; the esters rose from 10 per cent to 40 per cent of the total cholesterol;—there was no preoperative total lipid determination made; on the first postoperative day the total blood lipids were 1020 mg. per cent and during the first three weeks after operation they dropped to 613 mg. per cent; in the seventh postoperative week, total cholesterol was 235-279 mg. per cent (esters 43-53 per cent); total lipids, 694-915 mg. per cent. The values for the period of study with insulin withdrawal are listed in Table V. The blood levels during the thirteenth week were: cholesterol 210 mg. per cent (esters 43 per cent), total lipids 593 mg. per cent (last determinations).

These data are not complete enough to allow definite conclusions. They do show, however, some suggestive trends in Cases 1 and 2. In case 1 observations over the space of 40 weeks reveal a fairly consistent decline in the total lipids, and to a less extent in the total cholesterol. The very few determinations in case 2 would seem to follow the same direction. No such trend is noted in case 3; the cholesterol and total fat values did decline in the immediate postoperative period, but this change was merely a return from a very high preoperative level to a more nearly normal range (Fig. 7). There was a definite increase in the lipids during the

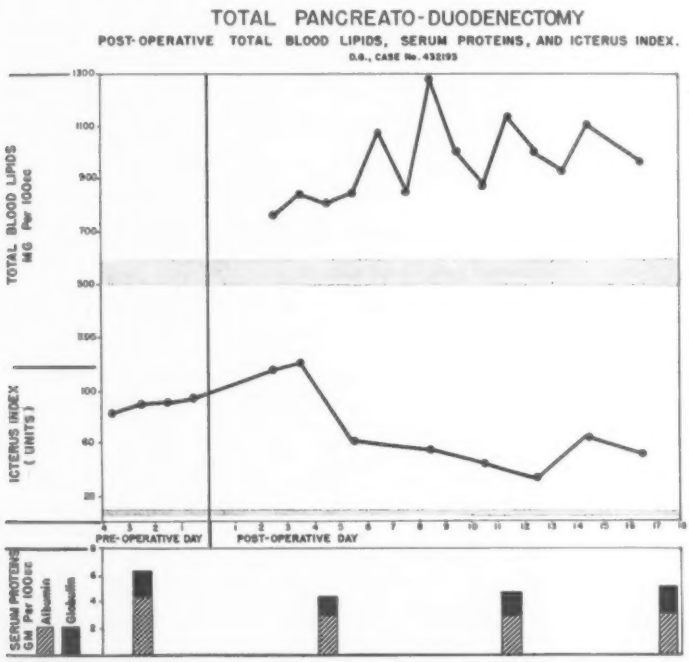

FIG. 8.—Changes in blood lipids and icterus index in a fatal case.

interval of insulin withdrawal and the presence of ketosis, but the most recent determinations were again normal.

Another observation on lipid metabolism should perhaps be recorded although it was made in a case not included in the present study. This patient died 18 days after total pancreatoduodenectomy for carcinoma of the pancreas. The cause of death, verified by autopsy, was hepatic insufficiency due to very advanced fatty degeneration of the liver. The patient's blood lipids became markedly elevated postoperatively and remained high until death (Fig. 8). In the same patient the icterus index also failed to return to normal although there was no mechanical obstruction to the flow of bile from the common duct into the jejunum. Identical observations on the behavior of the icterus index in at least two more cases of total pancreatec-

tomy have made us regard the icterus index as a good measure of the functional state of the liver in the immediate postoperative period; in the presence of a functioning choledochal stoma a rising index after the first three postoperative days suggests a failing liver. Whereas, in the case described above the hepatic failure was associated with fatty parenchymatous degeneration of the organ, in one of the other two cases such an association was not present, and in the third case autopsy was not done, and thus no conclusive evidence of the presencce or absence of such changes could be had. Nor can we be certain that the fatty degeneration of the liver in the case in question was etiologically linked with the interruption of the normal physiological function of the pancreas by the operation.

SUMMARY

After the presentation of short resumés of the clinical histories of three cases of total pancreatoduodenectomy, two of whom survived the operation for three and 14 months respectively, and one of whom is living and well four months after operation, observations are described on the early and late changes in the carbohydrate metabolism, on the alterations in the fat and protein digestion and absorption, and on the trends and significance of the blood levels of pancreatic enzymes, lipids and bilirubin in the depancreatized patient. The effects of the withdrawal for 72 hours of insulin in such a patient are reported.

CONCLUSIONS

(1). In the experience of the authors, the characteristics of the diabetes in patients after total pancreatectomy are (a) a relatively low insulin requirement (20-60 daily units); (b) a sensitivity to insulin, and (c) frequent and often unpredictable fluctuations in the bood sugar level.

(2). Because of these characteristics, the safe way of controlling the diabetes is to maintain the fasting blood glucose level on the hyperglycemic side (150 + mg. per cent).

(3). The ketosis that developed in a depancreatized patient after a 72-hour period of deprivation of insulin was comparable to a moderately severe ketosis in diabetes mellitus.

(4). An elevated basal metabolic rate renders the control of total surgical diabetes more difficult.

(5). There are suggestive evidences that the pathophysiology of total surgical diabetes is not identical with diabetes mellitus as understood in terms of the conventional clinical type.

(6). The means available to correct the consequences of the absence of the external pancreatic secretion are effective. The dosage of pancreatin recommended in the past for substitution therapy is probably high. Six to 8.0 Gm. of pancreatin (U.S.P.) daily in the cases observed was sufficient to

assure satisfactory fat digestion, and to maintain a normal state of nutrition and, in one instance, a positive nitrogen balance.

(7). Lipase and amylase are demonstrable in the blood stream for long periods of time after total pancreatectomy.

(8). No evidence of a deficiency of the lipotropic pancreatic factor was noted on a maintenance diet of high protein and average carbohydrate and fat content.

(9). No characteristic trends were observed in the changes of blood lipid values.

NOTE: The authors are greatly indebted to Dr. Oliver H. Gaebler, for his valuable and generous help with many of the problems of this study.

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Discussion.—Dr. Laurence S. Fallis, Detroit (closing): I have only one or two observations of practical importance to make. First, I should like to comment on the value of pancreatic enzyme studies preoperatively. We have found that the absence or marked reduction of pancreatic enzymes in the duodenal drainage, as described by Whipple and his associates, in conjunction with evidence of obstructive jaundice is strongly suggestive of carcinoma at the head of the pancreas. In six of eight cases recently observed, the impression gained was of help in establishing the differential diagnosis. There is also no doubt that the control of diabetes in these patients on the hyperglycemic side is by far the safer procedure. The objection may be raised that a long-continued hyperglycemic state hastens the degenerative changes so often observed in chronic diabetes, but of course none of these patients has survived over a sufficient period to prove or disprove that point. I should like to mention also that in the control of surgical diabetes the use of protamine zinc insulin has been of considerable advantage. Its long-lasting action more nearly approaches the even flow of the secretory mechanism of island tissue. But it still lacks the moment-to-moment adjustment that is so often necessary, and we have observed that even with protamine zinc insulin, control is difficult because of the unusually high insulin sensitivity.

COLORIMETRIC DETERMINATION OF AMYLASE*†

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A SIMPLE COLORIMETRIC method for the determination of amylase was devised because of the great importance of assays of this enzyme in clinical medicine and physiology. The significance of amylase in surgery has been abundantly demonstrated. Curiously, the conditions governing the determination of the activity of amylase have not been studied systematically, so that previous amylase methods have necessarily been more or less empirical and haphazard. The kinetics of this enzyme were examined critically by us and the results are included in this paper.

All methods for determining amylase have rested on one of three principles, the iodometric, saccharogenic or viscosmetric.

The iodometric principle was first advanced in quantitative form by Wohlgemuth in 1908.[1] Amylase activity was expressed in terms of the time required for a given enzyme sample to render a starch substrate colorless to iodine. Many modifications, based on this principle, have been used[2, 3] in an effort to reduce the subjective factor in color estimation. Since an excess of substrate must be present for optimal enzyme activity, an end-point which calls for total disappearance of the substrate is completely unsatisfactory. Most of the adaptations of this principle have, therefore, sought an end-point short of complete decolorization such as the point where the red color due to erythrodextrins takes the place of the blue of starch.[4] Redfern[5] introduced a glass color standard for comparison with starch-iodine colors before the achromic point is reached, but the technic is crude. The error of subjective color estimation has been the most important limitation of the iodometric principle.

The saccharogenic principle, now widely used,[4, 6, 7, 8] is based on measurement of the reducing groups produced by the hydrolysis of starch. Thus, by measuring the reducing power of the enzyme-substrate mixture before and after incubation one obtains a measure of enzyme activity. Reduction is measured by a copper method such as that of Shaffer and Somogyi[9] and results are expressed in terms of milligrams of glucose liberated. The accuracy of these methods is limited to materials in which initial reducing power is low. High blanks necessarily occur in diabetic urine and blood. Moreover, the preparation of the substrate in the valuable method of Somogyi[4] is inconvenient.

The viscosimetric principle, described by Davison,[10] depends upon the decrease in viscosity of the starch substrate as the average molecular size is

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† Read before the American Surgical Association, Quebec, Canada, May 27, 1948.

reduced by hydrolysis. Viscosity measurements are made in an Ostwald viscosimeter, the time required to reduce the viscosity by 20 per cent being taken as an expression of enzyme activity.[11] Elman and McCaughan[11] recommend this principle as the only means of measuring the full range of hydrolysis rather than the disappearance of substrate or the production of end products alone. The following sources of error are inherent in this method: the time of incubation is necessarily variable since viscosity change does not bear a linear relation to time; there is an initial change in viscosity which occurs with addition of the enzyme sample; further, the viscosity of the enzyme does not change during incubation.[12] Comparisons of the available methods have been made by several authors.[6, 12-16]

THEORY OF THE METHOD

Colorimetric methods are well suited to use in quantitative enzyme assays. If either the substrate or one of the reaction products is colored it may be measured directly in the photoelectric colorimeter. Also, reagents may be added to produce color with the substrate or a reaction product.

The blue color of the starch-iodine complex affords an opportunity to apply the second of these colorimetric procedures. Its depth with an excess of iodine was found by us to be strictly proportional to the amount of starch present.

A plot of the logarithm of the colorimeter reading against the arithmetic concentration of starch in the presence of a constant amount of iodine gives a straight line. By using this curve as a reference standard one may readily determine the amount of starch present in an unknown sample to within 0.02 mg.

Up to 4 mg. of starch with 4 ml. of 0.01 *N* iodine reagent will give colors which when diluted to 100 ml. can be conveniently read in the Evelyn photoelectric colorimeter, an instrument used in all of our work. A 660 millimicron filter eliminates all extraneous color such as that due to the excess iodine and to the dextrins formed in amylolytic hydrolysis. In this range a 100 per cent change in iodine concentration has only a slight effect on the color. In this way, measurement of the color given with iodine by aliquot samples of the starch-enzyme mixture before and after incubation permits enzyme activity to be expressed in terms of milligrams of substrate hydrolyzed.

Starches. The source and method of preparation of the starch influence its solubility, the stability of solutions, the initial reducing power, and the viscosity, as well as susceptibility to enzymatic hydrolysis.

We have found that high-grade potato starches are very soluble and uniform. Clear solutions give more intense colors with iodine per weight than any other starch examined and are of low viscosity, suggesting that this starch is composed of comparatively long, unbranched molecules. A soluble starch was, therefore, used throughout.

The Starch-Iodine Color. At neutrality the starch-iodine color is stable for many hours both in the dark and the light. We have confirmed the

finding of Swanson[17] that it gives a single peak absorption curve in the Beckman spectrophotometer having its maximum at 590 mu. The color disappears at alkaline pH values probably because the iodine is displaced from the starch molecule by hydroxyl ions. Dialysis of the complex removes the iodine completely in a few minutes, color being restored on addition of more iodine which is evidence that the bond between starch and iodine is a loose one.

KINETICS OF STARCH HYDROLYSIS BY AMYLASE

The kinetics of starch hydrolysis by amylase were investigated in order to outline proper conditions for an assay procedure. Fresh human urine was the source of enzyme.

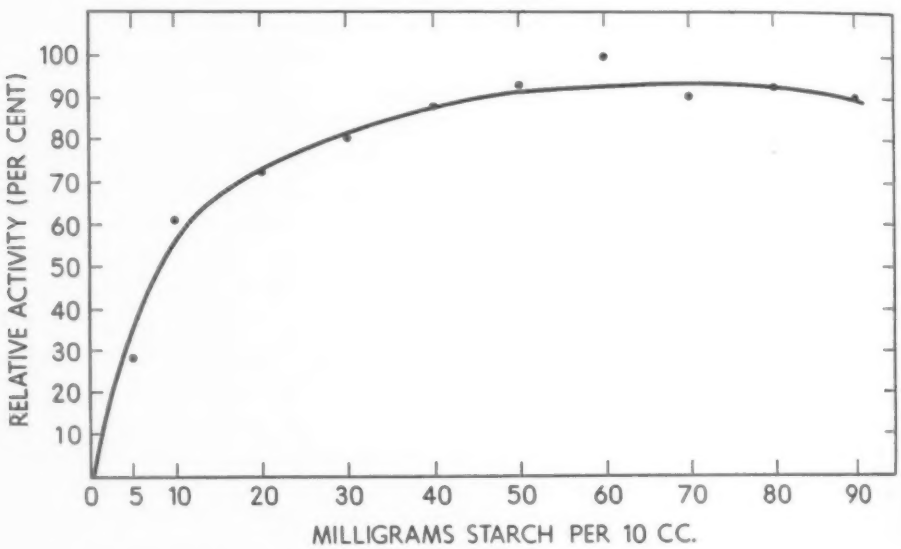

FIG. 1.—The effect of substrate concentration on the rate of enzymatic hydrolysis of starch. Progressive amounts of starch were incubated for on hour with a constant amount of enzyme and phosphate buffer at pH 7 and 37° C.

Effect of Substrate Concentration. A plot of substrate concentration against reaction velocity yields a typical curve (Fig. 1) showing that maximum velocity, or saturation of the enzyme with substrate, was reached at about 45 mg. per 10 ml. We therefore chose a substrate concentration of 80 mg. per 10 ml. for all subsequent work. In this range change in substrate concentration has a minimal effect on the velocity.

A quantitative expression of enzyme-substrate affinity which helps to characterize enzyme systems is afforded by the Michaelis and Menten constant,[18] most accurately found by plots of the reaction velocity with varying substrate concentrations according to the method of Lineweaver and Burk[19] (Fig. 2). Values for starch cannot be expressed in terms of molecular weight and so have been expressed in terms of milligrams per 10 ml. The

Michaelis and Menten constant for the starch employed by us, using a single enzyme concentration, was 7.14 mg. per 10 ml. This agrees well with the value of 7.9 mg. per 10 ml. found by Hanes[20] who used a saccharogenic method.

Effect of Enzyme Concentration. A linear relation between enzyme concentration and rate of hydrolysis is the most important prerequisite of any enzyme assay. Although the change in starch-iodine color is theoretically produced by only the initial steps in starch hydrolysis, this linear relation (Fig. 3) proves it to be an adequate measure of enzyme concentration.

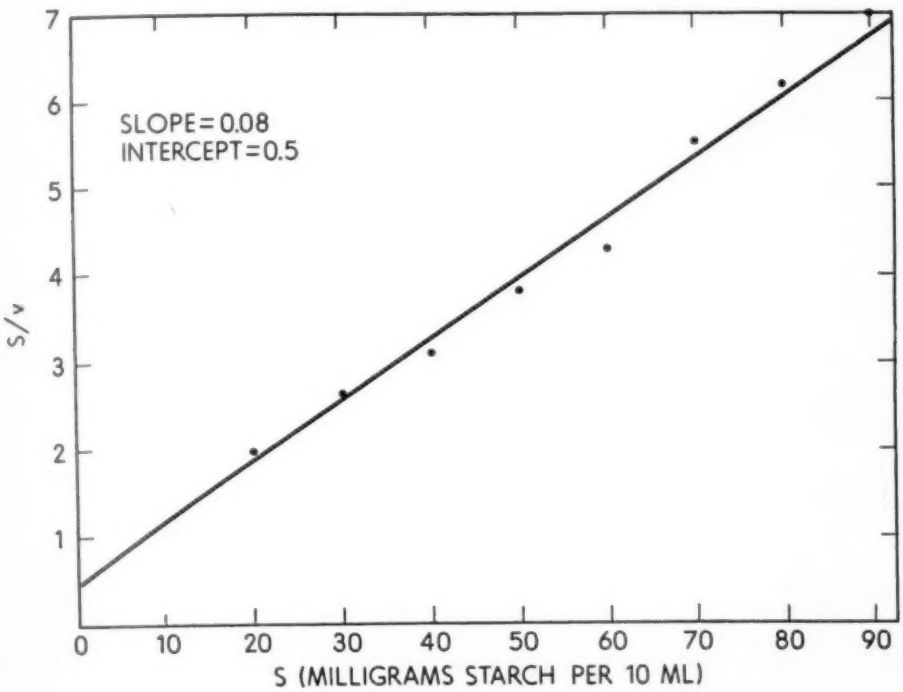

FIG. 2.—Data from Fig. 1 plotted according to Lineweaver and Burk. Substrate concentration, S, in mg. per 10 ml., is plotted against S divided by the velocity of hydrolysis, v, expressed as milligram of starch hydrolyzed per hour. From the intercept and slope of this curve the Michaelis and Menten constant was calculated to be 7.14 mg./ml.

Effect of Time. The time course of hydrolysis (Fig. 4) is linear, equal amounts of starch being hydrolyzed in equal times until the enzyme is no longer saturated with respect to substrate. The prediction from Figure 3 that the limit of saturation will be reached when about 35 mg. of the 80 mg. of starch is hydrolyzed is confirmed experimentally by the sharp decrease in velocity at this point. For this reason enzyme preparations are diluted so that not more than 35 mg. (44%) of the starch will be hydrolyzed in the allotted time. Kjeldahl[21] advised a 40 per cent limit of hydrolysis and Evans,[16] 30 percent.

pH Optimum. With some variation previous workers have found the pH optimum for amylase to be around neutrality.[22, 23, 24] At 37° C. we find the optimum to be at pH 7.4 (Fig. 5). Amylase, therefore, appears to be one of the few enzymes commonly found in the serum which exerts maximum activity at precisely the normal pH of blood.

Effect of Temperature. Roberts[2] found a flat range from 30 to 35° C. for the optimum of amylase activity. Kjeldahl[21] reported an optimum temperature of 48° C. and O'Donovan[24] described a "marked reduction" in activity after the enzyme was heated to 58° C. for 30 minutes. The temperature-

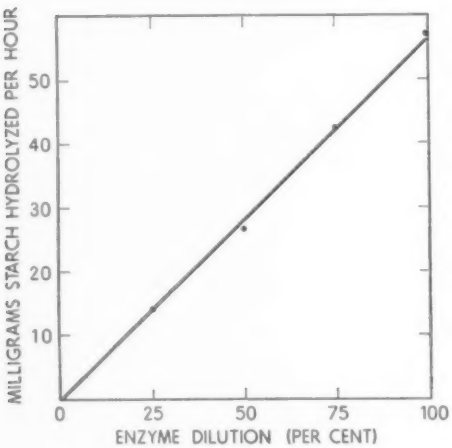

FIG. 3.—Effect of enzyme concentration on the rate of hydrolysis.

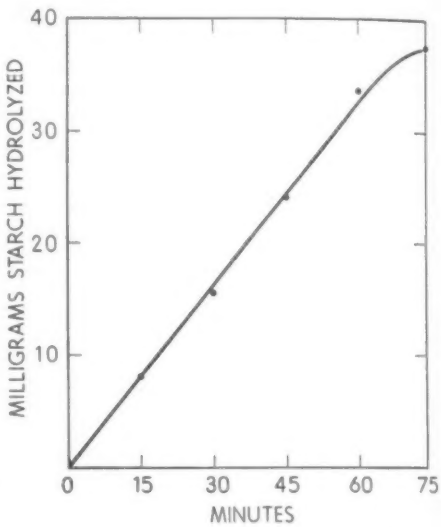

FIG. 4.—Time course of hydrolysis. The velocity decreases when the enzyme is no longer saturated with substrate.

activity curve, determined by our method (Fig. 6), puts the optimum temperature at 55° C.

Activators and Inhibitors. Activation of amylase by chloride ion has been observed by several investigators.[3, 22, 25-29].

The activity of dialyzed saliva is increased 3.8 times with sodium chloride in 3.42 millimolar final concentration. We have tested no smaller concentrations; however, the effect of increasing concentrations of sodium chloride is shown in Table 1. Wohlgemuth[30] observed activation in as low concentrations as 0.16 millimoles per liter (0.00097 per cent). The normal blood salt concentration of 105 millimoles per liter makes addition of salt unnecessary in an assay of undiluted sera. With dilution, however, we have found that the activity of serum falls off more than the calculated amount because of the fall in concentration of the chloride ion activator.

Enzyme samples with activity greater than that required to hydrolyze 35 mg. of starch per ml. of enzyme per hour must be diluted. To preserve

maximum activity dilution is performed with 0.9 per cent sodium chloride.

Activation of amylase by other substances, such as whole blood and tissue extracts, has been studied by Wohlgemuth[31] and O'Donovan.[24] This activity has been at least partly traced to proteins and amino acids by Rockwood[32] who also was the first to quantitatively determine the inhibiting effect of fluoride ion.[27] We have made use of the fluoride effect to inhibit the enzyme at the end of the incubation period, since acid inhibition precipitates the proteins in the enzyme sample carrying some color out of solution. A combination of fluoride ion inactivation, reduction to room temperature, and dilution are sufficient to stop the reaction. Fluoride ion is included in the Iodine Reagent described below.

TABLE I

Effect of Sodium Chloride Concentration on Amylase Activity of Dialyzed Saliva

Final Concentration of Sodium Chloride		Relative Amylase Activity in Percent
Millimoles per liter	Percent	
0	0	26.4
0.00342	0.02	100.0
0.00684	0.04	99.0
0.01710	0.10	83.2
0.03420	0.20	85.4
0.06840	0.40	85.8
0.13680	0.80	59.8
0.25650	1.50	76.2
0.42750	2.50	48.0
0.85500	5.00	42.1
1.71000	10.00	14.1

METHOD

Reagents

STARCH SOLUTION. A 2% stock solution is freshly prepared for each series of determinations. Weigh approximately 2 gm. of starch* in a 100 ml. beaker and suspend this starch in about 25 ml. of distilled water. Bring about 60 ml. of distilled water to a boil, pour rapidly into the starch suspension and transfer the contents quantitatively to a 100 ml. volumetric flask using hot water for washing. On cooling make the flask to volume with distilled water. This procedure yields 100 ml. of a 2% starch solution which is dissolved and almost water clear.

* The starch which we have found most valuable is Takamine Soluble Starch manufactured by Takamine Laboratories, Clifton, New Jersey.

Iodine Reagent. This is a solution of 0.01 Normal Iodine containing Potassium Iodide (0.3%) and Potassium Fluoride (5%). Weigh 13 Gm. of Iodine into a weighing bottle. Dissolve, according to the method described by Van Slyke,[33] about 30 Gm. of pure potassium iodide in about 250 ml. of water and transfer the iodine quantitatively from the weighing bottle to a 1 liter volumetric flask washing with the iodide solution. Add the remainder of the iodide solution to the liter flask and dilute the contents to the mark. This 0.1 *N* stock solution is standardized by titration with a standard sodium thiosulfate solution using a starch indicator; a deviation of 0.005 *N* is permitted. To make the final iodine solution 50 Gm. of potassium fluoride is weighed out and added to a 1000 ml. flask containing 100 ml. of the stock iodine solution and the contents diluted to the mark.

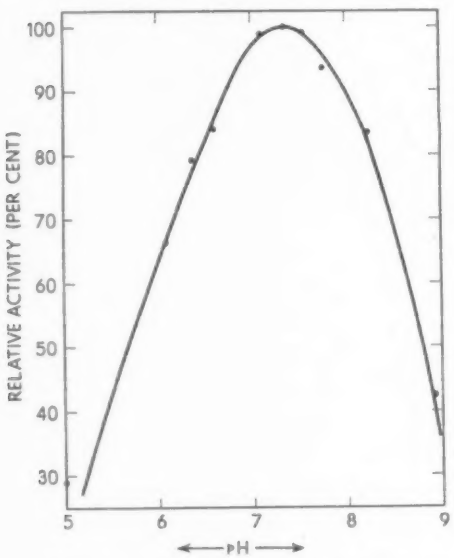

FIG. 5.—Effect of pH on the rate of starch hydrolysis by amylase. Activity is expressed in terms of per cent of the maximum.

This reagent is kept in a cool place in the dark or in a darkened bottle. Slow loss of iodine will occur but is not noticeable by titration with sodium thiosulfate for 3-4 weeks. If few determinations are to be made, it should be prepared in smaller quantities.

Phosphate Buffer. 0.04 *M* Sorensen's phosphate buffer, pH 7. Dissolve 3.471 Gm. anhydrous Na_2HPO_4 and 2.118 Gm. KH_2PO_4 in 1 liter of water.

The Standard Starch-Iodine Curve. Into each of a series of 100 ml. flasks containing 4 ml. of the iodine reagent is delivered progressive amounts of starch from 0.1 to 4.0 mg. Each flask is made to the mark and a sample of the contents is read in the Evelyn colorimeter in standard colorimeter tubes with a 660 millimicron filter.

The colorimeter readings plotted logarithmically against starch content will give a straight line which is used as the standard curve in all determinations. The concentration of the starch solution is checked daily before each test: Dilute 1 ml. of freshly prepared starch reagent to 100 ml. and compare the colorimeter reading of 5 ml. of this diluted starch in a 100 ml. volumetric flask containing 4 ml. of iodine reagent with the standard curve corresponding to 1 mg.

The Assay Procedure. Determinations are done in duplicate, tubes being incubated at 37° C. for one hour. For each sample to be assayed deliver 5 ml. of phosphate buffer and 4 ml. of starch solution into rimless test tubes and

stopper. For each tube prepare two 100 ml. flasks, each containing 4 ml. of the iodine reagent. Bring the test tubes to constant temperature in a stirred thermostatic bath at 37° C. Add 1 ml. of enzyme solution, appropriately diluted, from a blowout pipette to each tube; restopper the tube and invert to mix. Then immediately remove 0.5 ml. and transfer to one of the volumetric flasks; swirl the contents to assure maximal inactivation of the enzyme by fluoride ion.

Another 0.5 ml. sample is taken after one hour of incubation and treated

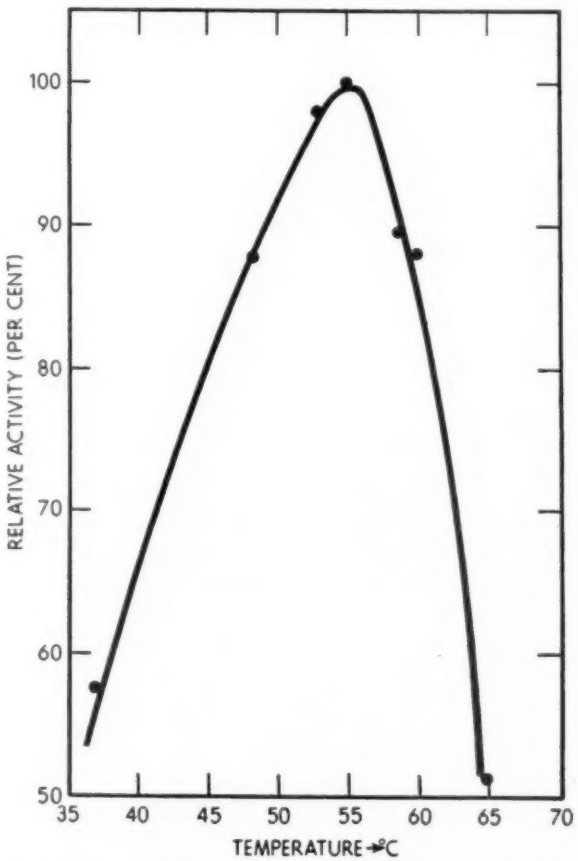

FIG. 6.—Effect of temperature on amylolytic hydrolysis.

similarly. The contents of the flasks are diluted to the mark with distilled water and an appropriate quantity is transferred to colorimeter tubes and read in a colorimeter with a 660 mu filter.

From the standard curve the amount of starch present in the aliquot removed before and after incubation is found. The initial aliquot is 1/20 of the total incubating volume and the final 1/19. Therefore, to find the

changes of total starch present in the incubating tube the initial figure is multiplied by 20 and the final by 19.

Results are expressed as units. One unit is that amount of enzyme which hydrolyzes 1 mg. of starch in 1 hour at 37° and pH7 in phosphate buffer provided that not more than 44% of the starch is hydrolyzed. In this paper units are expressed per 1 ml. of enzyme. Preparations of low activity may be incubated longer and a corresponding factor employed. Strong preparations with activity above 35 units must be appropriately diluted with 0.9 per cent sodium chloride as described above.

RESULTS

Normal Values. It has been reported[34] that normal human serum amylase levels vary as much as 200 per cent from one individual to another.

In a series of 50 normal persons values by the present method ranged from 9.2 to 34.9 units. The average of these figures was 18 units; standard deviation ±5.32. No variations with sex or age were found. Multiple analyses of a given individual, examined at different times, gave more constant results, usually remaining within 10 units of one another.

Random urine samples varied in activity from 24.3 to 76.2 units with an average of 52.8. Dehydration, by limiting fluid intake, causes a rise in urinary amylase concentration which closely parallels the rise in urine specific gravity. Diuresis has the reverse effect. The dependence of amylase excretion on renal function has been repeatedly demonstrated.[7, 25, 28, 35, 36] Our limited experience with nephritic specimens supports the findings of these authors, that amylase activity is increased in the serum and decreased in the urine with decreased renal function.

Serum amylase levels were studied more thoroughly in one specific disease, diabetes mellitus. Much work has been reported on this subject using all amylase methods. Opinion has extended from that of Myers and Killian[7] who observed a significant increase in the serum, to that of Somogyi[37] who found a decrease in 33.4% of 382 diabetic sera to a level equalled by only 4.1% of a similar normal group. With our method we have been able to confirm the observation of Somogyi that the amylase values in diabetes mellitus are usually abnormally low. Thirty-six diabetic sera had an average activity of 13.8 units with a standard deviation of ±3.61.

SUMMARY

A simple accurate colorimetric method for the determination of amylase is described and the kinetics of starch hydrolysis by amylase as measured by this method are presented. The finding of a reduction in serum amylase in diabetes has been confirmed as an example of an application of this technic.

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SURGICAL EXPERIENCES WITH EXTRAMEDULLARY TUMORS OF THE SPINAL CORD*

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THE PROGNOSIS FOLLOWING SURGERY in certain types of tumors of the spinal cord may be excellent. Those tumors in which the predominating cell type is a fibroblast, the meningiomas and fibroblastomas, do not invade the substance of the cord. Being attached to the adjacent meninges, they affect the cord by compression only. If they can be removed together with their attachments to the dura, arachnoid, or adjacent nerve sheaths, recurrence does not take place. And if surgical extirpation can be accomplished before irreversible damage has been done to the cord, impaired function will return to a remarkable degree. It is with this group of tumors, the intradural, extramedullary, fibroblastic tumors, their diagnosis, localization, and the results of surgical removal that this communication deals.

Since 1924, 108 tumors of this type have been recorded in the Neurosurgical Service of the University and Postgraduate Hospitals of the University of Pennsylvania and have been followed in the Tumor Clinic a sufficient length of time to warrant inclusion in this report. Of these 108 tumors, 78 were found in females, 30 in males, an unexpectedly high incidence of this type of tumor in women. The average age was 45.3 years, the youngest 10, the oldest 78. Twenty-four of these cases were in the cervical area of the cord, 70 in the thoracic, 6 in the lumbar cord, and 8 involved the cauda equina. In 10 cases the tumor showed an extradural extension, nine cases being situated in the cervical area and one in the high thoracic region. The completeness with which such tumors can be removed is shown by the fact that of the nine cases known to have died since operation, only two died of a recurrence. In three instances a recurrence was suspected but reexploration showed a damaged cord, and adhesive arachnitis, but no further evidence of the original tumor. In this group of 108 cases, 44 complete cures can be reported. Tables I, II, III, and IV should be consulted. In view of the rarity of recurrence after complete removal, these total recoveries can be considered permanent.

Originally the diagnosis and localization of spinal cord tumors was accomplished on the basis of neurologic findings alone, but since the introduction of lipiodol and other oils opaque to the roentgen ray, their injection has replaced careful and repeated neurologic studies for the determination of the level of the lesion. From the neurologic and neurophysiologic standpoint, this is to be regretted. Not only does this method eliminate much of the intellectual pleasure involved in reaching a diagnosis by neurologic methods alone, but also important neurophysiologic information is

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TABLE I

Spinal Cord Tumors
Intradural Extramedullary

108 Cases
Males 30
29 white — 1 colored
Females 78
Average Age 45.3 yrs.
Youngest 10 Oldest 78

TABLE II

Position of Tumor

Cervical	24	108 Cases
Thoracic	70	
Lumbar	6	
Cauda Equina	8	

Extradural Extension Tumor 10
9 Cervical 1 Thoracic

TABLE III

108 Cases
115 Laminectomies
Mortality 6
Mortality % Case 5.6 — Operative 5.2
3 operated for recurrence but none found
1 operated and recurrence removed
2 operated at wrong level (too low), but reoperated and tumor removed

TABLE IV

Complete Cures 44 Cases

1 yr.	2 yrs.	3 yrs.	4 yrs.	5 yrs.
2	4	5	2	3

6—10 yrs.	12	11—15 yrs.	10
16—20 yrs.	2	21—25 yrs.	7

TABLE V

Methods Used to Confirm Level Diagnosis

No Queckenstedt, No Oil	3
Incomplete Block Oil and Queckenstedt	6
Incomplete Block Queckenstedt, Complete to Oil	19
Complete Block Queckenstedt, No Oil Used	18
Complete Block Queckenstedt and Oil	62
Symptoms Increased by Lumbar Puncture	5

possibly being overlooked. But from the standpoint of the patient, determination of the level of the lesion by an opaque myelogram saves him time, thereby preventing further cord damage, and assures him that the laminectomy opening will be properly placed and no more extensive than is absolutely necessary. A lumbar puncture with the application of the Queckenstedt test is an essential part of the study of any spinal cord lesion. If a tumor is suspected and if the hydrodynamic reactions and chemical studies of the spinal fluid are not entirely normal, oil should always be introduced into the subarachnoid space of the spinal canal. Occasionally, as was evidenced in five cases in this series, a lumbar puncture plus removal of fluid for protein estimation and serologic studies causes a sudden increase in symptoms of cord compression. When this sequence of events occurs, immediate exploration is obviously indicated to prevent further cord damage. In our experience this aggravation of existing cord symptoms following a lumbar puncture only occurs in the presence of a tumor.

In this series of 108 cases, one or the other of these tests were applied in 105 instances. Table V shows the results. It appears that oil is the most accurate means of reaching a level diagnosis. The position of the tumors is given in Table II.

Since these lesions are all extramedullary, they are frequently in contact with or even spring from the sheath of a posterior root. Consequently root pain or a girdle sensation is a common early complaint. In 70 cases in this series, frank pain was the initial symptom and in 10 others, numbness or hypesthesia. In 28 cases motor weakness was noted as the first disability. The relation of the tumor to the dentate ligament seems to have a definite effect upon the development of symptoms. If the tumor arises from the dura anterior to the dentate, as the mass increases in size, it will be crowded against the anterior or anterolateral surface of the cord and prevented from compressing an adjacent posterior root. Consequently generalized pressure is made upon the cord and motor symptoms may predominate over sensory complaints. In 28 instances in which motor symptoms were first noted, the position of the tumor was anterior or anterolateral in 19, and posterior or posterolateral in nine. Conversely, in the 80 cases in which pain was the initial symptom, the tumor lay posteriorly or posterolaterally in 63. Of the 17 anteriorly placed tumors causing pain, 15 lay above the second thoracic segment, nine cervical and six thoracic. And of the nine cervical tumors anteriorly situated and producing pain, eight were "dumb-bell" tumors with an extradural extension along an emerging pair of spinal roots. The posterior root was involved at this point with consequent segmental pain. All tumors involving the cauda equina, eight in number, had pain as an initial symptom.

The cervical tumors comprise an interesting group. Among these 24 cases, six lesions were situated at the level of the foramen magnum. In two instances the tumors were so nearly intracranial that cerebrospinal

fluid circulation was impaired and a choking of the discs reported. Three fatalities occurred in this group. One case had already had respiratory embarrassment and although the tumor was removed, he died in a respirator. Another case died of pneumonia 72 hours postoperatively. A third case was in satisfactory condition until, on the third postoperative day, she was turned on her back and given fluid by mouth. She promptly vomited, most of the vomitus entered the trachea and she choked to death at once. In a fourth case recurrence was suspected in an anteriorly placed tumor. Reoperation after an interval of 3 years showed no recurrence but a marked arachnitis. Death occurred from respiratory failure some months later.

TABLE VI

Tumor in Cervical Area

Complete Paralysis to Complete Recovery 7

Average Time Symptoms	22 Months
Average Time Complete Paralysis	10 Weeks
Average Time to Complete Recovery	18 Months

Tumor in Thoracic Area

Complete Paralysis to Complete Recovery 9

Average Time Symptoms	26 Months
Average Time Complete Paralysis	6 Weeks
Average Time to Complete Recovery	14 Months

No Postoperative Improvement 13

Average Time Onset Symptoms	34 Months
Average Time Complete Paralysis	7 Months
Average Time Follow-up—2 yrs.	5 Dead

All Tumors in Thoracic Area

A fifth case lived a semi-invalid existence for 6 years and was reported to have died of heart failure. The sixth case is alive 3 years postoperatively and has made a complete recovery. In the postoperative care of a patient who has had a tumor removed from the uppermost levels of the spinal cord, respiratory paralysis is an ever present danger. A respirator should always be in readiness, or at least a laryngoscope or other necessary instruments for tracheal intubation. The immediate, postoperative passage of a stomach tube is a wise precaution to keep the stomach empty and to provide measured nourishment. These patients should be nursed in the prone position on a cerebellar frame so that all secretions can drain freely.

A problem not infrequently encountered in spinal cord surgery is the completely paralyzed patient. Is operation worthwhile under such conditions? What criteria do we have to indicate the advisability of surgical intervention? Sixteen cases, seven in which the tumor was located in the cervical area, and nine in which the tumor was in the thoracic area, had total spastic paraplegia of the legs, loss of sphincter control, and a complete or almost complete sensory loss below the level of the tumor. In the cervical group of

tumors, (7) the average period from the onset of symptoms to the operation averaged 22 months; the period of complete paralysis averaged ten weeks. In the thoracic group of tumors, (9) the average time of duration of symptoms was 26 months, and of complete paralysis, six weeks. Yet all these cases made complete recoveries; the cervical in an average time of 18 months after tumor removal, the thoracic after 14 months. All have resumed work. Thirteen other cases were completely paralyzed and showed no postoperative improvement. The average duration of symptoms prior to surgical intervention was 34 months, and with complete paralysis, seven months. The average follow-up time in this unimproved group is two years. Five are known to be dead. All these tumors were located in the thoracic area with a single exception in the cervical region. It seems evident, therefore, that a case with a spinal cord tumor who has been completely paralyzed for two months has better than an even chance for recovery, if the tumor can be removed without further damage to the cord. (Table VI.)

In this group of 108 cases, six are postoperative deaths, 44 are completely cured, and 13 completely paralyzed, five of whom are known to be dead. What of the 45 cases remaining that do not fall into any of these categories? Four are known to be dead of intercurrent disease. Twenty-eight are improved, but not working, 16 are unimproved with the same partial disability as they had before the tumor was extirpated.

CONCLUSIONS

A tumor within the spinal canal, intradural and extramedullary in position, has a definite clinical history, pain, paresthesia, paralysis. Segmental pain is the first symptom, followed by sensory change and slowly developing motor weakness below the level of the lesion. The presence of a tumor should be expected if interference with cerebrospinal fluid hydrodynamics and chemical components can be demonstrated. Confirmation of the diagnosis and determination of the level of the lesion can be had by the injection of opaque oil. Unless the symptoms of cord compression have been allowed to progress unchecked for too long a period, the chances for improvement or even a complete cure, following surgical removal of the tumor are excellent.

DR. GILBERT HORRAX, Boston: I think Dr. Grant has done well to call our attention to these tumors and to summarize his experiences with a series of cases over a long period. Most of us have realized that extramedullary spinal cord tumors are extremely favorable tumors. I think Dr. Grant has brought out one fact very clearly; that is, that even though patients have had paralysis for a long time they are still capable of coming back to a perfect, or nearly perfect, result. In our series we have had 60 patients with 61 tumors—one had two tumors, which is rather unusual—and our statistics agree almost entirely with his as to sex and age and so on, the great majority being females and the age range running from 18 to 71. We also have used in recent years in a large proportion of the cases, some contrast medium to designate the level of the growth more distinctly than could be found by neurologic means. We have used oxygen a good many times, but also lipiodal or pantopaque.

(Slides) We have had what we would call good or excellent results in 44 cases, 72 per cent. These end results are, with a few exceptions, for a period of about four years. I am quite sure that when we get a complete followup our good or excellent results will be improved, because I think as years go on there will be further improvement; that seems to be one characteristic of these tumors, that improvement comes over a period of years, not just over a few months. We had one death in this group, and one case we could not follow.

This chart is interesting. There were 45 neurofibromas. On a purely arbitrary basis I have taken cases which had symptoms for twelve months or less to see whether duration of symptoms had any relation to results. In 85 per cent of patients who had symptoms for less than a year we had good or excellent results, but of those with symptoms for as long as five years with severe pain or paralysis, there were no good results. It is possible that an occasional case will show a better result over a period of years. On the other hand, if the weakness had not gone on to paralysis we had some with excellent recovery.

That is really about all there is to say from my standpoint, except to remark that surgeons in general and neurosurgeons in particular have recognized that they are very favorable tumors, ever since Sir Victory Horsley took out the first one in 1887, in which he got a perfect result. I think Dr. Grant has been very wise in studying this series so that he would know exactly what the situation was and how well they did, sometimes coming from complete paralysis to a perfect result.

THE CONTROL OF ANOXEMIA DURING SURGICAL ANESTHESIA WITH THE AID OF THE OXYHEMOGRAPH*

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IN A 1939 PRESENTATION to the American Surgical Association, entitled "Anoxia—A Source of Possible Complications in Surgical Anesthesia," McClure and associates[1] reached the conclusion that, "Full consideration of anoxia as a source of surgical complications should reduce preoperative narcotics to a minimum, promote the use of anesthetics which allow adequate oxygen in the inspired air, and emphasize the necessity of maintaining the blood pressure and respiration at near normal levels." "Further Anesthesia Studies with the Photoelectric Oxyhemoglobinograph"[2] were presented to this association in 1940. This communication emphasized the fact that the slow laborious method of following the oxygen saturation of the blood by means of repeated arterial punctures and gas analyses was not a practical procedure for clinical work especially as applied to anesthesia where immediate minute to minute results were essential for the guidance of the surgeon and the anesthetist in the prevention of operative and postoperative complications associated with anoxia. The application of the photoelectric cell technic, as suggested by Kramer [3, 4] and Matthes [5, 6] in 1934 and 1935 in experimental procedures, was described in the use of an imported Kramer apparatus and an instrument of our own construction which was a complete innovation including a vacuum type photocell, radio amplification and ink recording. The possibility of employing the photoelectric technic for blood oxygen saturation in clinical work by means of the portable, sensitive oxyhemoglobinograph was demonstrated for the first time.

In medical and dental practice the fields of narcosis and anesthesia are obviously the ones where most can be done in the prevention of anoxia Closely allied and frequently associated is the shock syndrome which usually implies severe anoxia.

Although the exact mechanism of narcosis remains controversial, the logical approach seems to be that of Warburg[7] and Quastel[8]—tissue respiration. The recent work of Schmidt[9] and Himwich[10] and their associates on pentothal anesthesia suggests that a part of the narcotic mechanism is a histotoxic anoxia, as demonstrated by a depression of the cerebral cellular respiration. If this theory of narcosis is accepted, it is obvious that some degree of anoxia may be an inevitable complication of anesthesia. The objective of the anesthetist, then, is to control anoxia within safe reversible limits in order to avoid irreversible pathological changes on the one hand and light narcosis with increased hypersensitivity on the other.

* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

The successful control of anoxia depends primarily on its prevention or early detection. Of the four types of anoxia, the one most readily recognized is anoxic anoxia, i.e., anoxemia. It is caused by an impaired oxygenation of the arterial blood at the lungs and is characterized by cyanosis and a generalized oxygen lack in all the tissues of the body. The occurrence of arterial anoxemia during anesthesia has been confirmed through objective observations as well as by chemical analyses.

It is an established fact that the human eye is subject to inaccuracies in so far as visual impressions of color are concerned. The interpretation of color varies not only from one individual to another but also in the individual response to the same color at different times. The development of photoelectric methods has afforded a means of proving this point conclusively. Comroe and Botelho[11] have recently reported that visual impressions of cyanosis are unreliable. They evaluated the ability of observers to detect cyanosis in 20 normal males, subjected to various gas mixtures, by a comparison of their color estimations with known arterial oxygen saturations, as obtained photoelectrically with the Millikan oximeter. Cyanosis was not detected by the majority of the 127 observers until the blood oxygen saturation fell to approximately 80%; while 25% of the observers were unable to recognize cyanosis even when the arterial oxygen saturation fell to levels of 71-75%. The authors point out that serious grades of arterial anoxemia may pass unrecognized by many physicians unless arterial blood is analyzed for oxygen content and capacity.

In the light of these findings, it is clear that the anesthetist requires instantaneous and accurate information concerning the degree of arterial oxygenation of the patient, if he is to fulfil his objective. Chemical analysis, which is a tedious and time-consuming procedure, offers no immediate aid. Consequently, he has had to rely on the changing color, blood pressure and pulse of the patient. The photoelectric oxyhemograph, recently described by Hartman, Behrmann and Chapman[12] should solve this problem for the anesthetist and allow him to supplement his observations with an accurate, continuous record of arterial blood oxygen.

It is the purpose of this presentation to describe the development of the oxyhemograph briefly and to show data which will prove the value of the instrument in the control of anoxemia in anesthesia.

Although the first photoelectric estimation of oxyhemoglobin is attributed to Nicolai [13] in 1932, the fundamental work in blood oximetry was performed by Kramer [3, 4] and Matthes [5, 6] each working independently. Kramer recorded variations in oxyhemoglobin *in vitro* and *in vivo,* using a method based on the spectral differences of hemoglobin and oxyhemoglobin in the red wave length region (620-770 mu). He showed that Beer's law of optical absorption may be applied to hemoglobin solutions and hemoglobin in the red cell. Matthes' contribution was the continuous registration of light absorption in different spectral regions, using red light for oxygen content

and green light for the total hemoglobin. In 1935 Matthes[6] adapted Kramer's method[4] for closed blood vessels in the experimental animal to human beings, using an ear lobe attachment.

After using an imported Kramer apparatus, Hartman and McClure[2] developed a one-color instrument which operated in the red wave length region. This "oxyhemoglobinograph" consisted of a photoelectric colorimeter in which the beam of light passed through the web of the hand. Although the apparatus provided the desired sensitivity for clinical studies, its most serious limitation arose from volume changes in the tissue thickness exposed to the light beam, thus introducing an error.

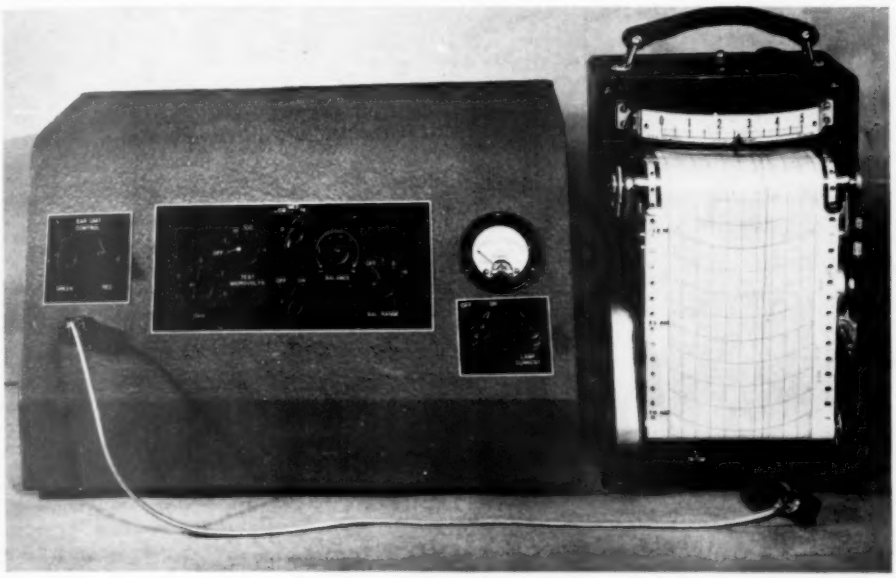

FIG. 1.—The oxyhemograph.

Matthes[5], Squire[14], Goldie[15], and Millikan[16] have appreciated the disturbance created by volume variations and have attempted to correct for it in their photoelectric methods for blood oxygen determination. Although the technical details vary, all of these methods involve photocell recordings in two spectral regions, one sensitive to total hemoglobin (near infrared, Squire; blue, Goldie; green, Matthes and Millikan) and the other, the red wave length, which is sensitive to oxyhemoglobin. Squire and Goldie standardized their instruments by rendering the tissue bloodless, whereas Millikan compared the fully flushed ear with an optical filter. Of these three methods, only the Millikan oximeter reached the production stage and, therefore, it was used extensively in the war-time aviation research program.

The oxyhemograph (Fig. 1) has incorporated within it the best features of the technics described in earlier publications. It is the result of the joint endeavor of workers from the Department of Laboratories, Henry Ford Hospital, and the Research Laboratories Division, General Motors Corpora-

tion, Detroit, Michigan. The blood oxygen saturation is measured through the use of a bichromatic photocell as registered through the ear, a unique feature of the method being the amplification by means of a "contact-modulated" D.C. amplifier, which is stable and sensitive and allows a permanent, continuous record on a rugged D.C. milliameter.

The ear unit* (Fig. 2) contains two miniature photocells, a small lamp,

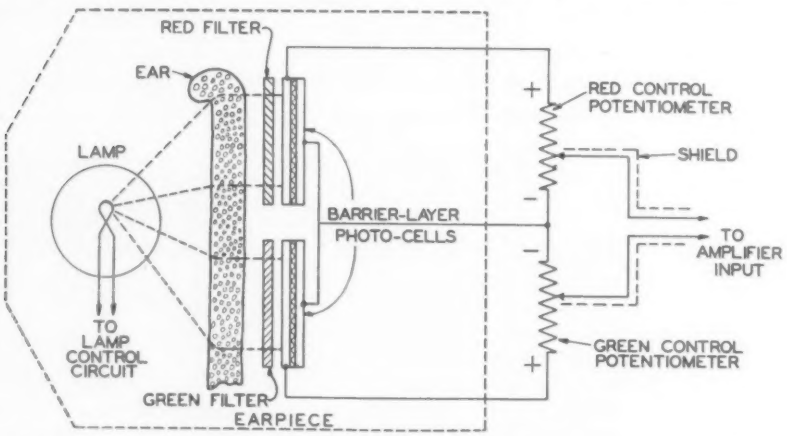

FIG. 2.—Circuit diagram of the photo-electric ear-piece and control potentiometers.

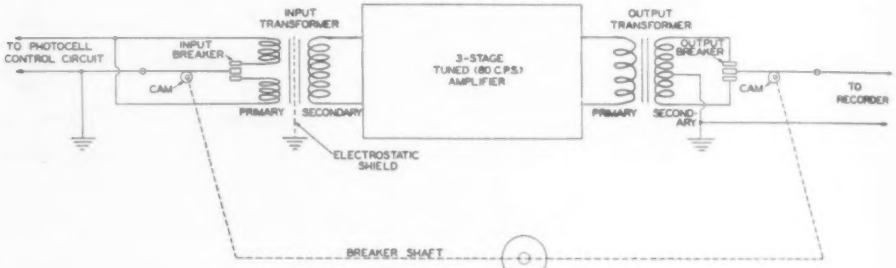

FIG. 3.—Block diagram of the amplifier unit.

and two color filters. Light transmitted through the ear is measured in two spectral regions. The "red" cell photocurrent reflects changes in the oxygenation of the blood together with volume variations.** The "green" cell photocurrent reflects only volume variations because in this spectral region

* Coleman Electric Co., Maywood, Ill.

** The expression "volume variations" includes four variables: (1) tissue thickness which affects the amount of light absorption by the tissue itself; (2) extent of the capillary bed which affects the amount of blood in the optical path; (3) total hemoglobin which affects the amount of hemoglobin in the optical path; and (4) vasomotor changes, caused by fluctuations in blood pressure which would affect factor (2), and associated at times with a redistribution of hemoglobin, as may occur in shock, which would affect factor (3).

the absorption characteristics of oxyhemoglobin and reduced hemoglobin are similar. The two photocurrents are opposed to one another so that changes due to volume variations are largely canceled out, allowing only the signal measuring an oxygen change to be emitted. This difference signal is changed to alternating current, is amplified, rectified and sent to a milliameter which makes an ink record of blood oxygenation (Fig. 3).

The instrument was calibrated by correlating actual arterial blood oxygen saturation values with the oxyhemograph readings (Fig. 4). The blood was analyzed in duplicate for oxygen content and oxygen capacity, using Van Slyke's manometric method. The per cent saturation was computed from these figures. Data obtained on 20 patients under pentothal—N_2O—O_2 anesthesia show that the chemical and instrumental data are usually within ±2½%. The conformity of the blood values and the oxyhemograph are proof of its reliability.

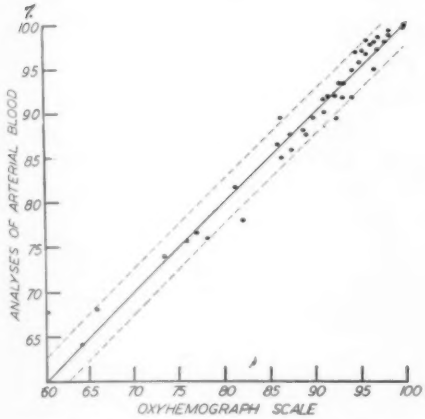

FIG. 4.—Correlation between the chemical and instrumental values for the blood O_2 sat. in %. Identical value fall on the solid line. 28 out of 42 points (66.6%) lie within ±1%. Those points (39 out of 42 or 92.8%) included within the broken lines represent an agreement of ±2½%. The remaining points (3 out of 42 or 7.2%) are within 3-8%.

The sensitivity of the oxyhemograph permits a tracing of the fluctuations in the oxygenation of the blood associated with the respiratory cycle. This is well demonstrated not only in the experimental animal (Fig. 5) but also in the anesthetized human (Fig. 8). Such a rapid response should make the instrument a boon to the anesthetist, for the first warning of developing anoxemia is registered much earlier than can be appreciated by clinical observations.

Oxyhemography was employed in a series of operations requiring one half to ten hours of anesthesia. Each record included blood oxygen saturation curves during the preanesthesia period in room air, the induction, and the fluctuations, occurring throughout the surgical anesthesia. Records were obtained under various types of anesthesia, as follows: pentothal, pentothal—N_2O — O_2, cyclopropane, ethylene and ether, and spinocaine anesthesia.

PENTOTHAL

The current widespread usage of intravenous anesthesia, together with the variance of opinion as to the necessity for coincident oxygen administration, prompted the early work carried out with the oxyhemograph. It seemed that a continuous record of blood oxygen should offer information, otherwise impossible to obtain under the short-acting barbiturates. As the study progressed, the combination of pentothal — N_2O — O_2 was included because

of its extensive use in surgical anesthesia. Both experimental* and clinical subjects were used in these studies.

Clinical data was acquired on 20 orthopedic cases, subjected to pentothal, pentothal — O_2, or pentothal — N_2O — O_2 anesthesia, of a duration ranging from 17 to 218 minutes. The preoperative medication consisted of ¼ to ⅙ gr. of morphine sulfate and 1/150 gr. of atropine sulfate. The pentothal was administered by the intermittent technic of Lundy and varied according to the individual's sensitivity to the drug. The total dose ranged from ½ to 1¾ gms. The inhalation anesthesia was administered by face mask in the usual manner. Although a 50-50 N_2O-O_2 mixture was preferred, the effects of altering the ratio of N_2O to O_2 on the blood O_2 curve were obtained. Two arterial punctures were obtained during the anesthesia for calibration of the curve. Gas samples were drawn from the rebreathing bag for analysis to verify the N_2O-O_2 mixture administered.

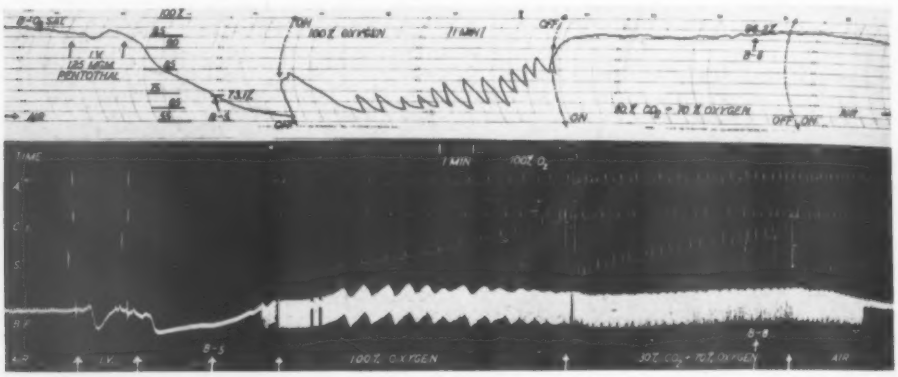

FIG. 5.—Simultaneous tracings of blood O_2 saturation in % (B—O_2 sat.) time in fifths of a minute, abdominal (A) and costal (C) respiration, spirometer (S) record of pulmonary ventilation and blood pressure (B.P.) on a dog, subjected to pentothal anesthesia are shown. (B-5) and (B-6) represent analyses of arterial blood. An intravenous (i.v.) injection of 125 mgm. of pentothal under room air conditions caused a cessation of the respiration which created a marked decrease in the blood O_2 saturation from 97% to 52%. The slow recovery of 100% O_2 is graphically depicted by the tracings. As the expiratory phase of each respiratory cycle is completed, an immediate upward swing of the oxyhemograph pointer to a peak, followed by a fall until the end of the next respiratory cycle is observed. It is possible to align each wave in the tracing with a breath. The administration of a 30-70 CO_2—O_2 mixture increased the rate and depth of the respiration, thus smoothing out the oxyhemograph tracing. On return to room air, a more regular respiration rate was able to maintain normal blood oxygenation.

A comparison of three types of pentothal inductions illustrates the value of O_2 therapy in intravenous anesthesia (Fig. 6). In the bone graft case, the induction was performed in air. The blood O_2 fell from 87% saturated to 68% saturated after the patient had received 16 cc. of 2½% pentothal. The insertion of the airway, followed immediately by a 50-50 N_2O-O_2 mixture, caused the blood O_2 to become 98% saturated within three minutes. Changing the mixture to a 26-74 ratio of N_2O-O_2 had no effect on the blood

* To be published.

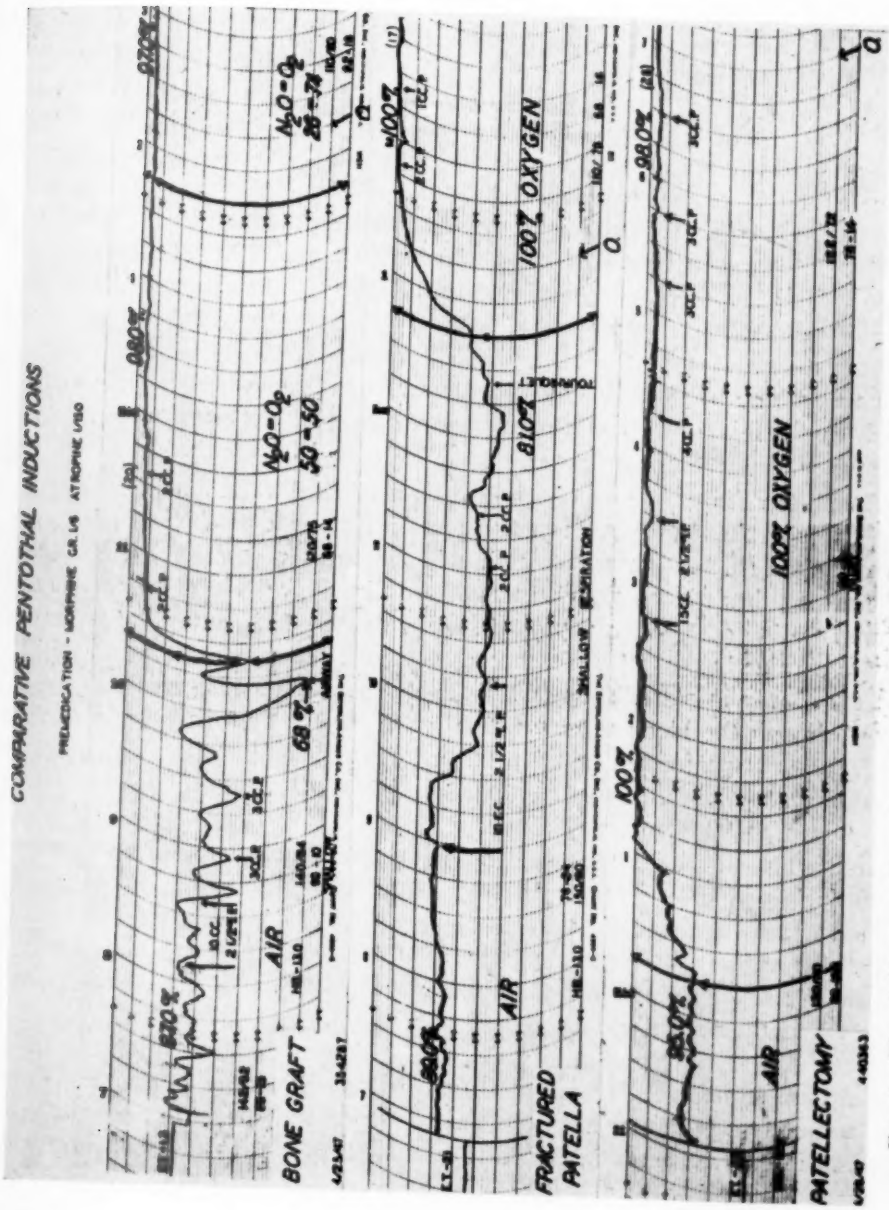

FIG. 6.—Figs. 6-14 are self explanatory. The following abbreviations have been used: (P) pentothal, (O) open wound, (C) close wound, (O') zero time, (E.T.) ear transmission value, (0.5 A) type of filter used, (150 M.A.) amperage of light source, and (G-6) amplifier gain control setting, (A) airway, (B) blood analysis.

O_2 level. This kind of induction is probably the most common procedure used in pentothal—N_2O-O_2 anesthesia. The second induction was carried out on a patient to be operated on for a left, comminuted fracture of the patella. The blood O_2 fell from 89% to 81% in air after an administration of 14 cc. of 2½% pentothal. The administration of 100% O_2 brought the blood O_2 level to 100% saturated within two minutes. The third case, a patellectomy, shows a room air blood O_2 value of 95% saturated, followed by the administration of 100% O_2. The pentothal was not administered until the patient had breathed O_2 for five minutes, at which time the O_2 had reached a value of 100% saturated. Although 28 cc. of pentothal was necessary, the blood O_2 saturation showed no change, maintaining the high level of 98% to 100%. This comparison shows the definite advantage of high O_2 concentrations during the induction period and during the maintenance of anesthesia. The 50-50 N_2O-O_2 mixture apparently is as efficient as 100% O_2 and has the advantage of reducing the pentothal requirement. It is important to reach maximum oxygenation at the beginning of the anesthesia as it is easier to maintain this level than to bring it about after a period of pentothal anesthesia.

In all barbiturate anesthesia one finds a marked variation in individual sensitivity to the drug. A 51-year-old male, a chronic alcoholic, underwent an orthopedic operation for comminuted fractures of the tibia and fibula. The preanesthesia blood O_2 level was 88% (Fig. 7), but after an intravenous administration of 10 cc. of 2½% pentothal the blood O_2 saturation fell rapidly to a value below 60%. On noting the blood O_2 decrease, the anesthetist put the airway in place. Then with difficulty the patient was given 100% O_2, thus bringing the blood O_2 saturation up to 99%. The major part of the operation was performed under pentothal supplemented by a 50-50 N_2O — O_2 mixture. The latter part of the operation shows that the blood O_2 was maintained at 92% saturated under a 60-40 N_2O — O_2 mixture. Shortly after the tourniquet was removed the patient breathed room air for 7 minutes, during which time the blood O_2 fell to 82% saturated. Although the wound had been closed the patient was kept in the operating room for further observation since he showed early cyanosis. After 6 minutes of O_2 the blood level rose to 87% saturated but, with the return to room air, removal of the patient's mask and airway, the blood O_2 saturation fell gradually to 62% within 9 minutes. This chart indicates that sensitivity to pentothal may be observed in the induction period. It may give a warning of the amount of pentothal a patient may tolerate and may even suggest the extent of the hypoxemia in the postoperative stage.

Organe and Broad[17] first used the combination of pentothal — N_2O —O_2 anesthesia to obtain relaxation that is impossible with N_2O alone and to avoid the prolonged depression caused by large doses of pentothal. They used an 85-15 mixture which reduced the pentothal requirement to slightly more than half the usual dosage. At present proportions of N_2O — O_2

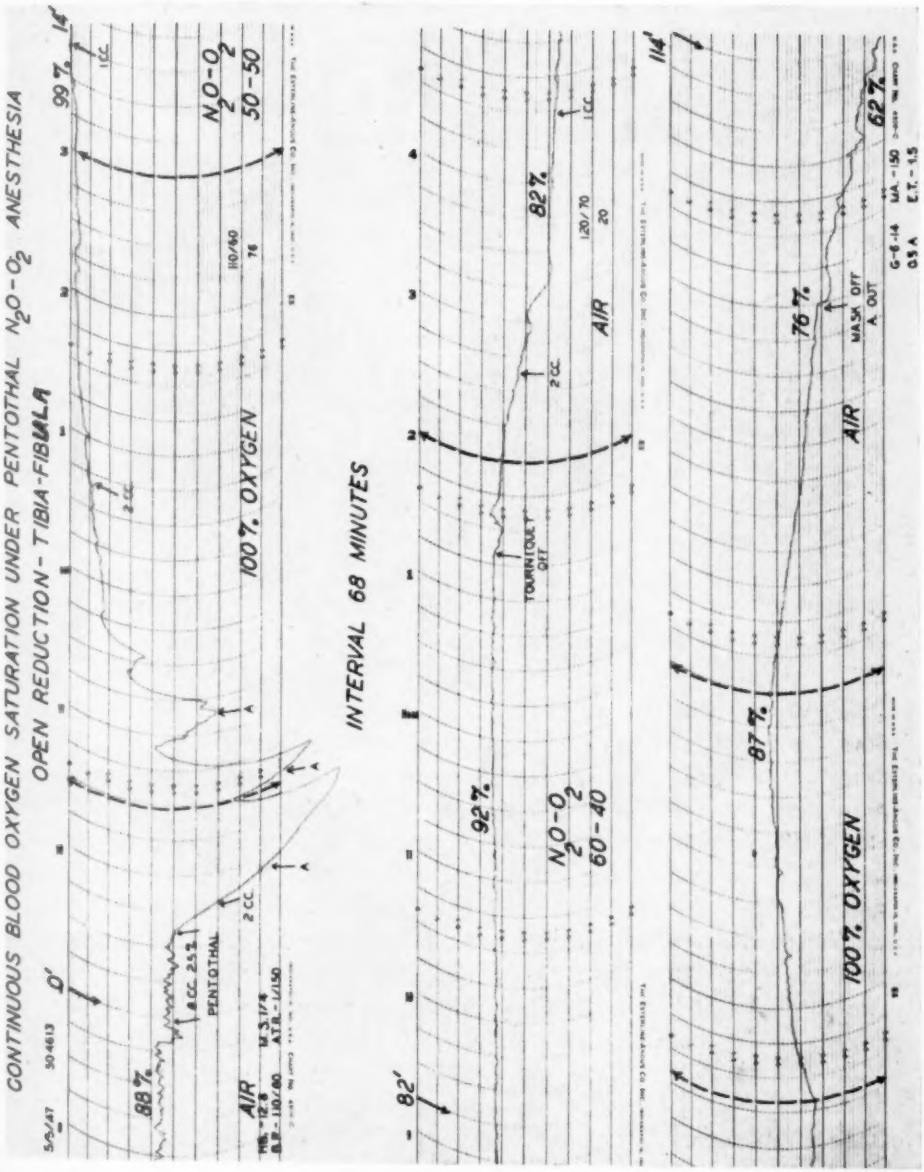

FIG. 7.
(See Figure 6 for legend.)

ranging from 85-15 to 50-50 are in use, although the 50-50 ratio is favored for it insures adequate oxygenation as well as a reduction in the pentothal requirement. Leake and Hertzman[18] and McQuiston, Cullen, and Cook[19] have reported that N_2O — O_2 mixtures alone, below the 80-20 ratio will cause extreme anoxia. Therefore, we studied blood O_2 values under pentothal supplemented by N_2O — O_2 mixtures in proportions ranging from (0-100) to (90-10).

The oxyhemograph tracing taken on a 44-year-old male (Fig. 8), while a patellectomy was performed under pentothal — N_2O — O_2 anesthesia, gives typical data of the degree of blood oxygenation when the inspired O_2 is decreased by 10% increments. The blood O_2 fell from 93% to 77% in the induction period. Typical respiratory waves emphasize the sensitivity of the oxyhemograph. These fluctuations show actual changes in the blood O_2 saturation coincident with each respiratory cycle. The blood O_2 remained between 97% and 100% so long as the O_2 in the N_2O-O_2 mixture was above

TABLE I.—*Summary of Blood O_2 Saturation Values under Pentothal Anesthesia, Supplemented by Varying Proportions of N_2O — O_2*

N_2O — O_2 %	Number of Administrations	Range of Blood O_2 Values % Saturation	Average of Blood O_2 Values % Saturation
0-100	39	81-100	94
25-75	6	76-100	95
30-70	5	88-100	95
40-60	4	93-100	97
50-50	26	69-100	95
60-40	8	78-100	94
66-33	3	85-100	93
70-30	9	67-99	86
75-25	6	88-99	93
85-15	5	58-78	67
90-10	5	35-68	53

30%. Within the last 10 minutes of the operation the patient breathed room air for 2½ minutes, during which time the blood O_2 fell to 93.4% saturated, as checked by an arterial puncture. The reduction of the N_2O — O_2 mixture to an 84-16 ratio caused the blood O_2 to drop rapidly from 97% to 64% within 5¼ minutes. This type of curve occurred in every instance in which the O_2 administration was less than 20%. At the end of this operation we obtained a graphic recording of the commonest danger of the postanesthetic period. The patient had been breathing O_2 for about one minute previous to the removal of the mask and his transfer from the operating table to the stretcher when the chin dropped and the tongue blocked the pharynx. The blood O_2 fell rapidly from 97% saturated to 58% saturated within 2¼ minutes but when the anesthetist's attention was called to this depression of the O_2 record, simply lifting the patient's chin with restoration of the air passage allowed the blood O_2 to return to normal. This record should prove valuable in impressing all concerned with the need for alertness in protecting the patient during the immediate postoperative period.

Table I summarizes the data on blood O_2 saturation over the entire range of N_2O — O_2 mixtures used in conjunction with pentothal. It is clear that in N_2O — O_2 mixtures in which the O_2 value is 30% or more, the blood

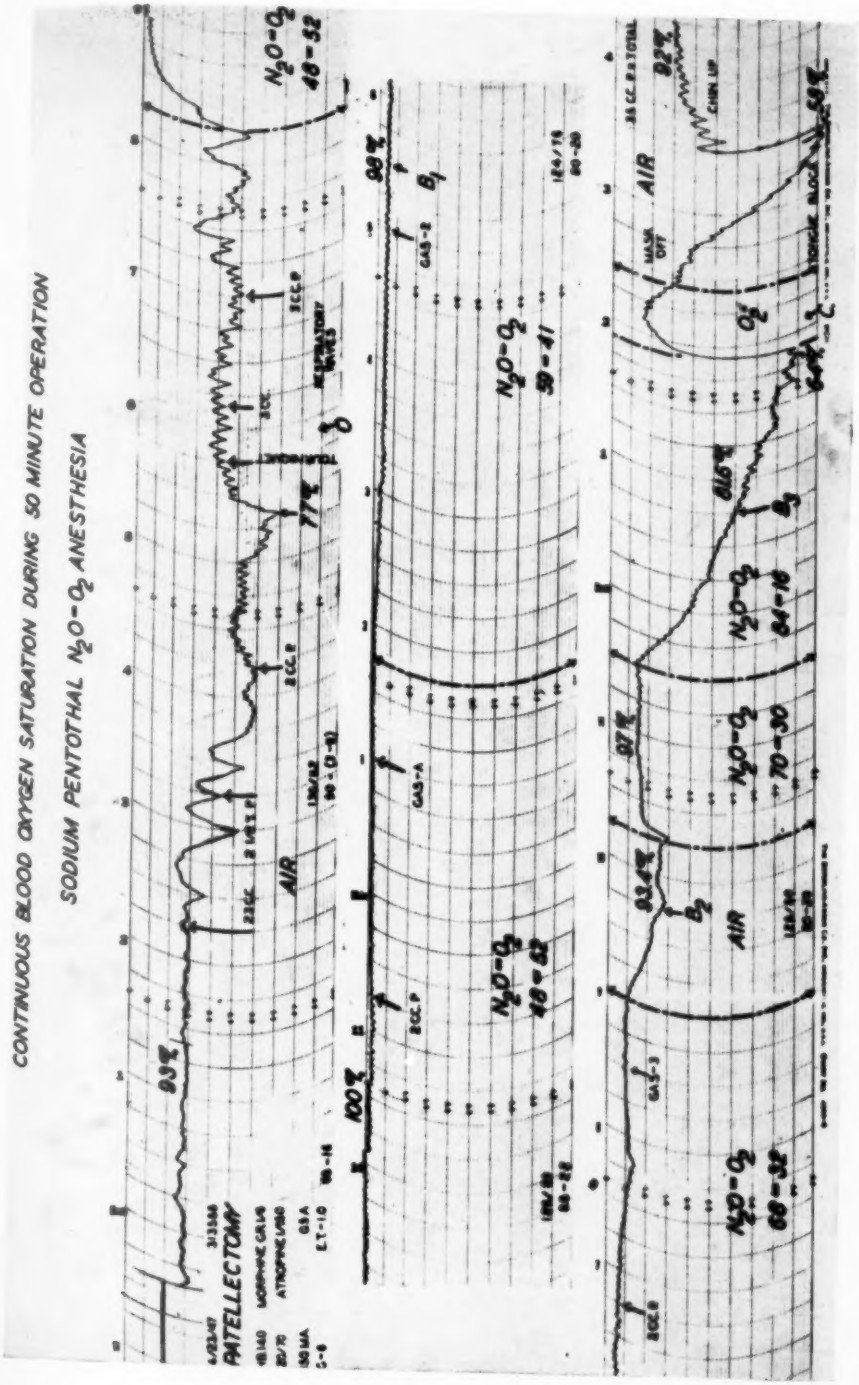

FIG. 8.
(See Figure 6 for legend.)

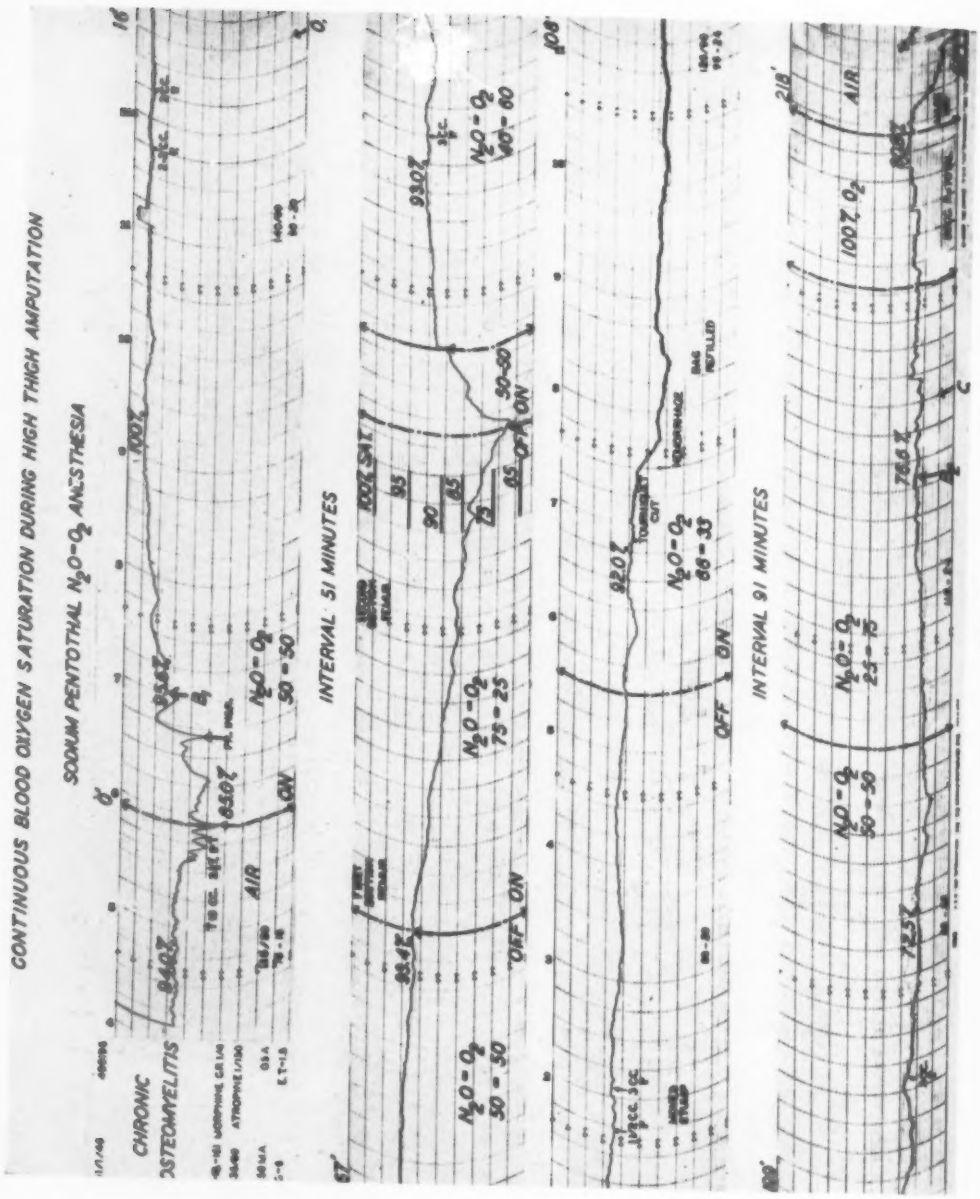

Fig. 9.
(See Figure 6 for legend.)

oxygenation is maintained at 93% saturated or above. If, however, the O_2 content of a N_2O — O_2 mixture is 25% or less, hypoxemia appears. The average blood O_2 saturation value obtained with the 75-25 N_2O — O_2 ratios was 86%. This is, of course, on the borderline between safe oxygenation and hypoxemia. However, it should be noted that the range of values obtained was from 67% to 99%, dependent largely upon the pentothal dosage. In the 10 instances in which the O_2 inspired was 15% or less, severe hypoxemia occurred. This is proven by the fact that the entire range of blood oxygen values recorded was below safe levels. The average blood O_2 saturation of 67% in the 85-15 N_2O — O_2 mixtures and 53% in the 90-10 N_2O — O_2 mixtures are definite proof that the 85-15 N_2O — O_2 mixtures used by Organe and Broad are too low in O_2 and usually cause serious anoxia.

An analysis of the data shows that patients receiving as much as 1¾ Gm. of pentothal over periods up to two hours, maintain a blood O_2 level above 90% so long as the O_2 administered is above 40%. Even 100% O_2 is not adequate for normal oxygenation in operations lasting over two hours. This is well demonstrated in Fig. 9, which depicts an oxyhemograph recording during a high thigh amputation on a 23-year-old male who was suffering from chronic osteomyelitis. A normal induction, followed by the usual increase in blood O_2 under a 50-50 N_2O — O_2 mixture, is shown. As the tracing is followed during the second hour of anesthesia, it may be noted that a 75-25 N_2O — O_2 mixture caused the blood O_2 saturation to fall from 93% to 66% within a nine minute period. An increased O_2 administration (60%) brought the blood O_2 value back to 93% saturated. Toward the end of the second hour the tourniquet on the stump was released. Hemorrhage occurred and obviously some unoxygenated blood was returned to the circulation. This period is characterized on the O_2 saturation record by an immediate drop in blood O_2. It is worth emphasizing that, from this point on, the blood O_2 never returned to a normal level, possibly because the shock syndrome was appearing at this time. In the fourth hour of anesthesia the blood O_2 was 72.5% saturated under a 50-50 N_2O — O_2 mixture. An increase of 25% in the O_2 inspired raised the blood level to 76.6% saturated as checked by an arterial blood analysis. At the close of the operation the administration of 100% O_2 increased the O_2 saturation only as high as 81%. In the postanesthesia period the blood O_2 fell rather sharply to 58% — 60% saturated. This anoxemia was clinically confirmed by the patient's ashen gray perspiring facies.

In N_2O — O_2 mixtures containing less than 40% the blood O_2 level fell below 90% after ½ hour of anesthesia with pentothal dosages as low as ¾ Gm. N_2O — O_2 mixtures containing less than 20% O_2 caused the blood O_2 to fall to 78% or lower within two-to-four minutes with pentothal administrations as low as ½ Gm. One exception in this series, a borderline anemia (Hb. — 10.7 Gm.) patient, showed values lower than 90% even on 100% O_2 and therefore suffered severe anoxemia under the N_2O — O_2 ratios containing lower O_2 percentages. The patient, of course, showed no skin

(See Figure 6 for legend.)

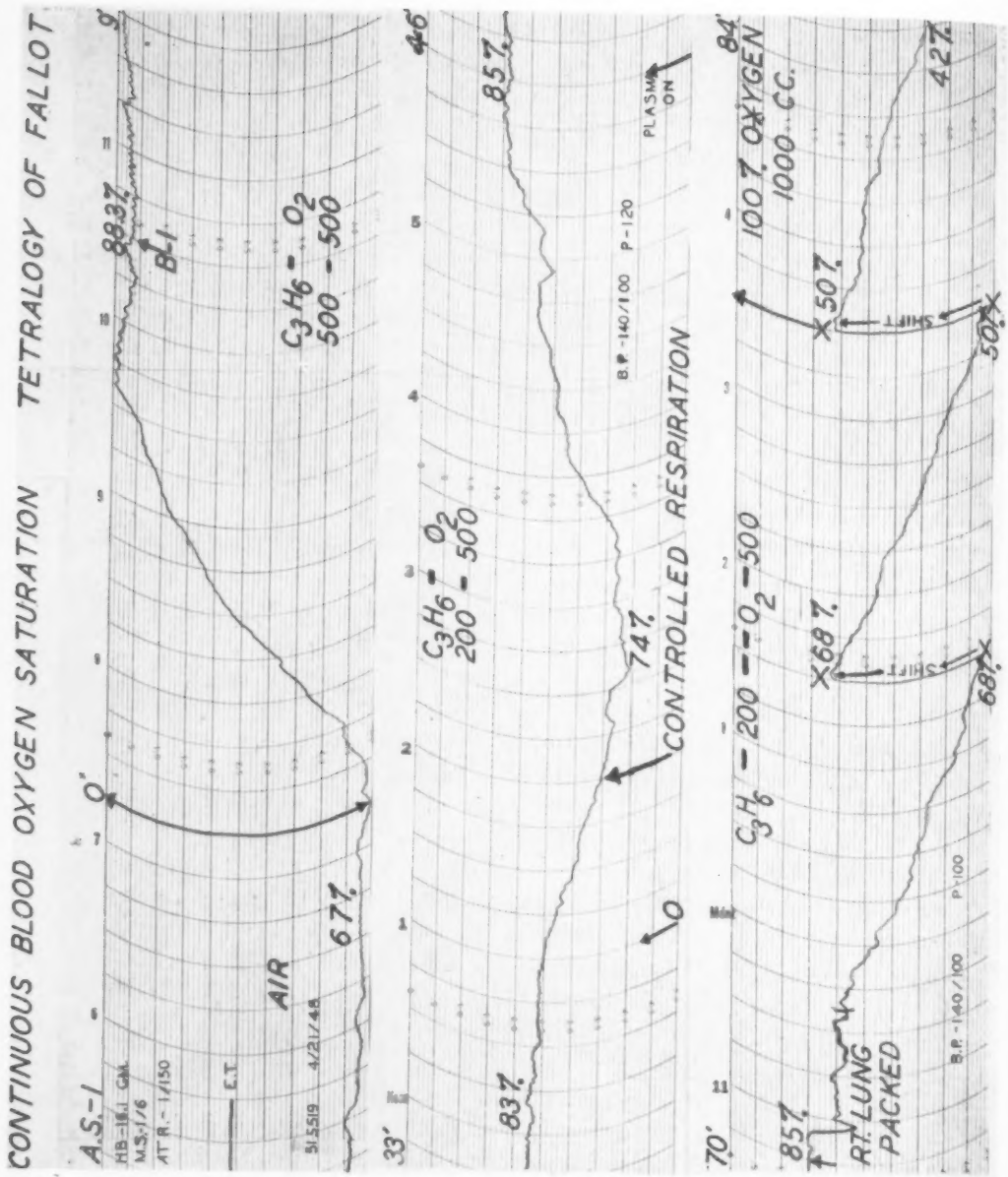

FIG. 10.
(See Figure 6 for legend.)

discoloration for she did not have the 5 Gm. of hemoglobin in the unsaturated state essential for cyanosis at any time.

CYCLOPROPANE

Oxyhemograph tracings were obtained under C_3H_6 — O_2 anesthesia under different types of operations. The cholecystectomy, pneumonectomy, and the Blalock operation were studied. A 500-500 proportion of C_3H_6 — O_2 resulted in blood O_2 values between 95% and 100% in patients with normal hemoglobin. These blood levels were usually maintained unless there was a fall in blood pressure.

Seven Blalock operations* have been studied. Typical data, (Figs. 10 and 11) obtained on a 23-year-old girl who had undergone a Blalock anastomosis, now non-functional, on the left side 18 months prior to the present operation, are shown. She had a left diaphragmatic paralysis. The patient's hemoglobin was 16.1 Gm., since a local physician had subjected her to frequent blood-letting in an attempt to alleviate the polycythemia. Preoperative medication was morphine sulphate, gr. ⅙, and atropine sulfate, gr. 1/150. The preoperative blood O_2 level was 67% saturated, as proven clinically by a definite cyanosis. The induction with a 500-500 C_3H_6 — O_2 mixture, brought the blood O_2 level to 88% saturation within five minutes. This was maintained for about ½ hour. After the chest was opened the blood O_2 showed a decrease from 83% to 74%. As the blood O_2 level was falling the anesthetist started controlled respiration, which showed a beneficial effect on the O_2 curve within four minutes, after which the blood O_2 level rose steadily to 85% saturated. At the beginning of the second hour the right lung was packed. This created a severe anoxemia, the blood O_2 saturation falling from 85% to 42% saturated within 12 minutes. The blood pressure also fell over this same period from 140/100 to 65/42. The anesthetist switched the patient to 100% O_2 with no apparent improvement, the blood O_2 remaining in the region of 40% saturated for several minutes. During the period not shown in the figures 2 minims of adrenalin were administered intravenously with the result that the blood O_2 rose to 45% for a period of two minutes, after which it dropped back toward 40%. Whole blood was administered, and within the next 45 minutes the blood O_2 saturation rose to 50%. The blood pressure gradually returned to 140/90 during the same period. For the four hours preceding the completion of the anastomosis in the sixth hour of anesthesia the patient's blood O_2 fluctuated between 45% to 50% saturated.

The dramatic increase in blood O_2 is effectively shown by the oxyhemograph at the removal of the clamps after the completion of the end of the subclavian artery to the side of the pulmonary artery anastomosis (Fig. 11). The beneficial effect of inflation of the right lung, of closing the chest and of natural respiration is also recorded. The blood O_2 saturation had reached 89% prior to the removal of the mask. The return to room air is especially

(See Figure 6 for legend.)

* To be published.

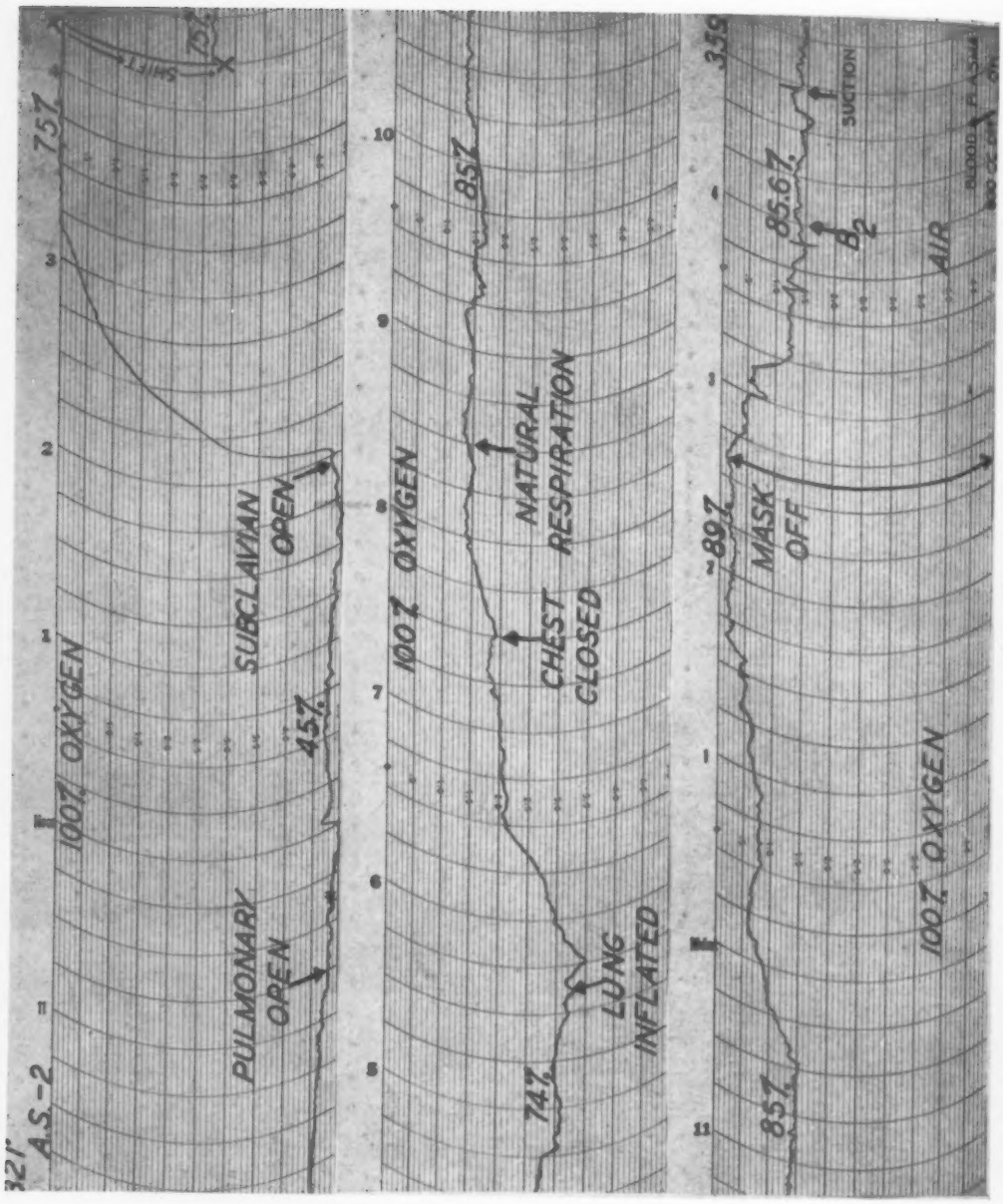

FIG. 11.
(See Figure 6 for legend.)

CONTINUOUS BLOOD OXYGEN SATURATION ABDOMINAL HYSTERECTOMY

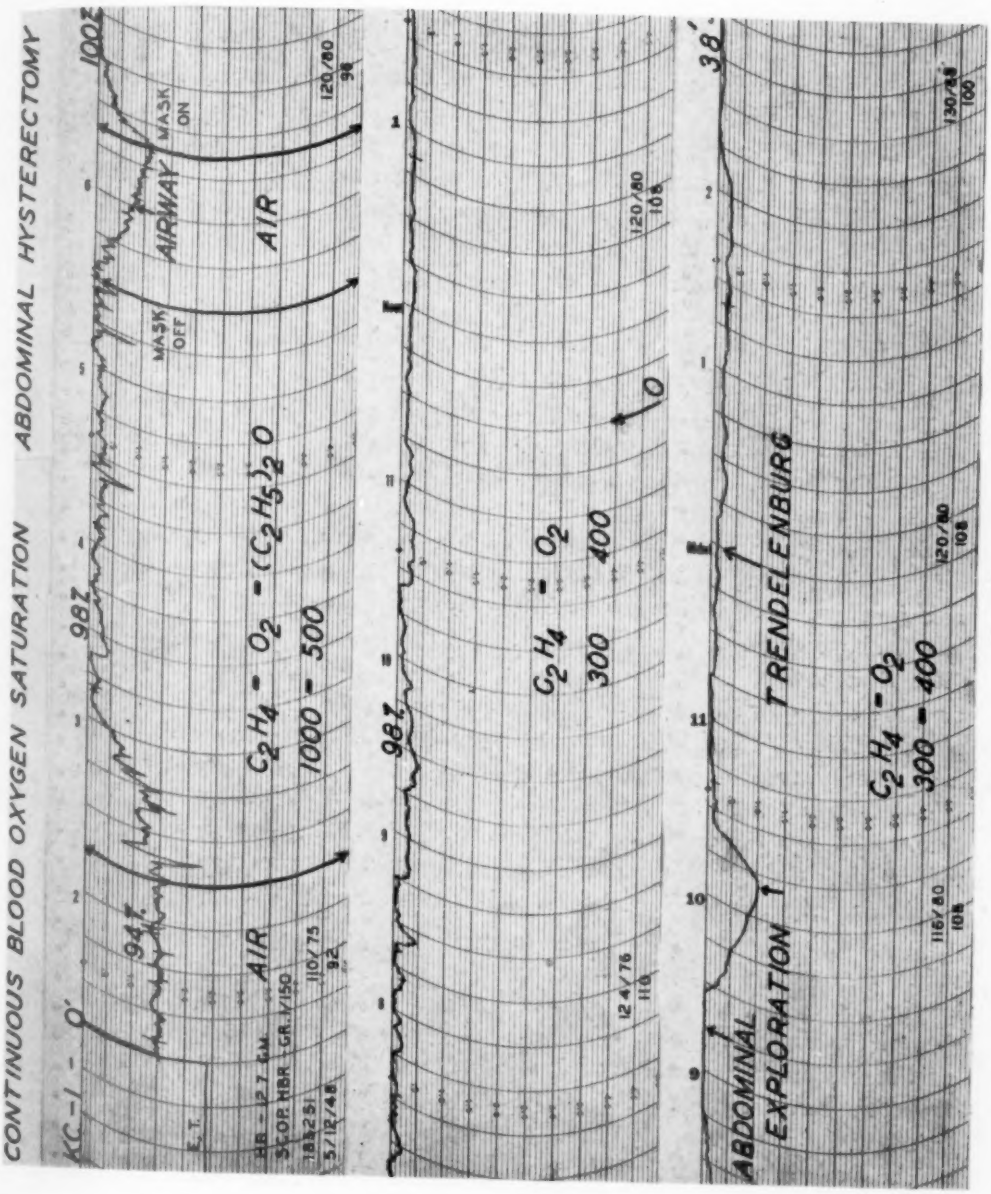

FIG. 12.
(See Figure 6 for legend.)

significant because it shows a blood O_2 drop of only 4%, in marked contrast to the induction record (Fig. 10). The marked improvement in pulmonary circulation and blood oxygenation effected by the anastomosis is well illustrated.

ETHYLENE AND ETHER

Three operations in which C_2H_4 and $(C_2H_5)_2O$ were administered as the anesthetic have been studied with the oxyhemograph. In each case the blood O_2 was maintained throughout the major share of the operation at normal or above normal values. Two of these operations were complete abdominal hysterectomies, whereas the third was performed for multiple fecal fistulae. The Trendelenburg position, employed in the three cases, created no change in the blood O_2 level at its institution. However, as the horizontal position of the table was restored in 10-15° stages, slight depressions in blood O_2 and blood pressure were noted.

A typical induction on one of the hysterectomies is shown in Figure 12. The blood O_2 saturation rose from 94% in air to 98-100% in the C_2H_4—O_2—$(C_2H_5)_2O$ mixture. The drop in blood O_2 saturation while the mask was off for the airway insertion is clearly illustrated. The remainder of the chart demonstrates that the blood O_2 saturation remained near 100% except during a manual exploration of the abdomen. The point at which the Trendelenburg position was assumed is also indicated. The effect of returning the patient to the horizontal position, while breathing a 300-400 C_2H_4— O_2 mixture is shown (Fig. 13). This was done after 68 minutes of anesthesia as the wound was being closed. The blood O_2 showed an immediate decrease which was alleviated by 100% O_2 inhalation. The blood pressure showed a slight fall during this same period. On breathing room air, the patient's blood O_2 saturation fell to 75%. Further inhalation of O_2 did not alleviate the hypoxemia appreciably. An administration of a 25-75 He — O_2 mixture had no beneficial effect, nor did O_2 under increased pressure. Although the operation was completed within this period, the patient was kept on the operating table about 16 minutes for further observation. Inspiration of room air caused the blood O_2 saturation to fall to 65% whereupon a 100% O_2 inhalation and an intravenous 5% glucose in physiological saline injection (300 cc.) were carried out. The blood O_2 curve reached the low level of 60% saturated, as shown by the tracing, until manual compression of the breathing bag was carried out by the anesthetist for 2 minutes. This forced ventilation seemed to have a beneficial effect because the blood O_2 saturation rose rapidly to 85% and then gradually fell toward 80% as the patient was aroused.

The final stage of another abdominal hysterectomy is shown in Figure 14. The decrease in blood O_2 and in blood pressure created by a 15° rise from the Trendelenburg position is observed. The effect of leveling the table as well as the return to room air created a gradual decrease in blood O_2 saturation from 90% to 56%. While the blood O_2 was decreasing the blood pressure fell from 118/80 to 90/70. When the arterial puncture (blood O_2 —

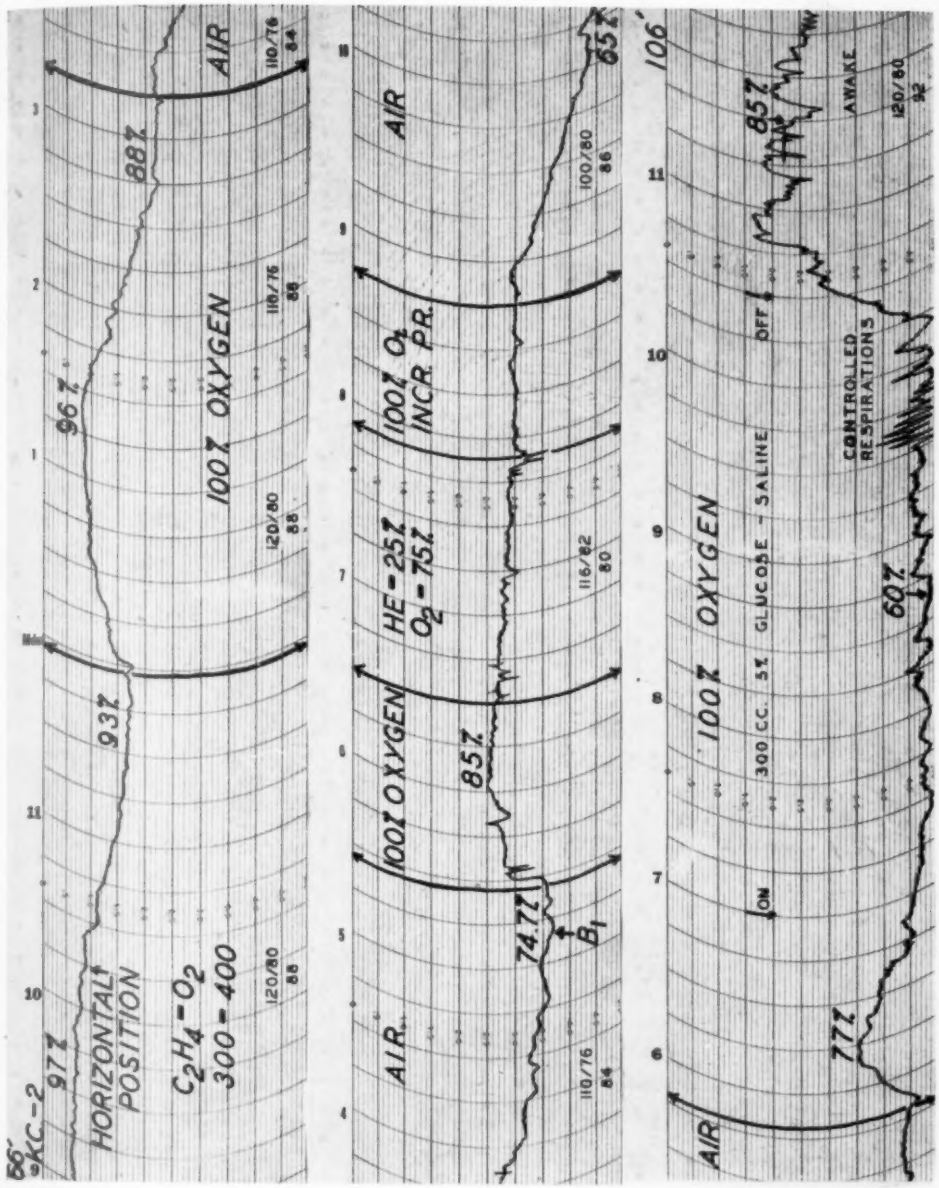

FIG. 13.
(See Figure 6 for legend.)

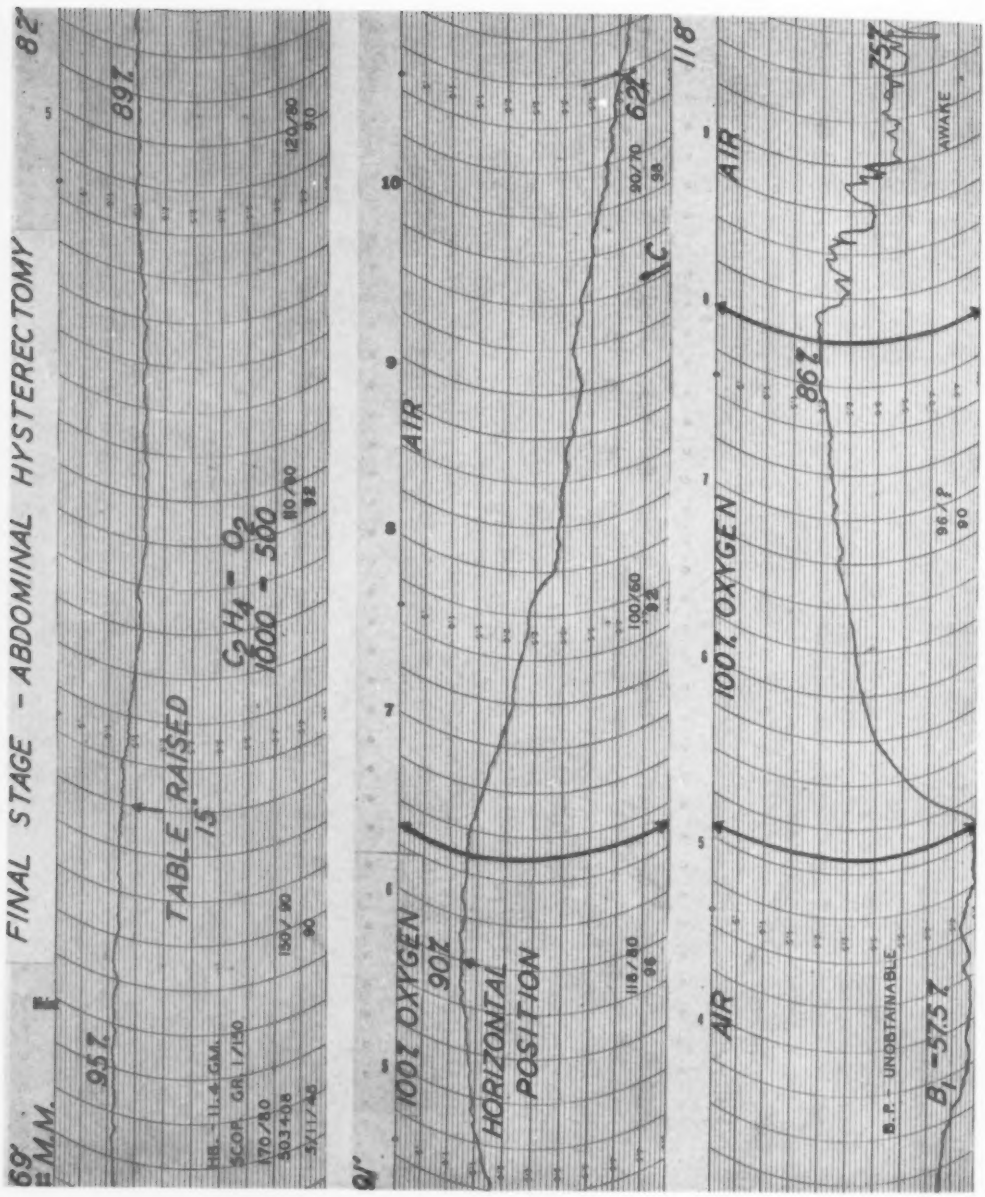

FIG. 14.
(See Figure 6 for legend.)

57.5% saturated) was done the blood pressure was unobtainable. O_2 inhalation brought the blood O_2 to a level of 86% saturated and the systolic blood pressure to 96 within two minutes. On return to room air the patient showed only a 75% blood O_2 saturation as she awakened.

It is significant that the fall in blood pressure so closely parallels the blood O_2 decrease. The fact that the blood pressure was obtainable after O_2 was administered for two minutes suggests that O_2 lack may be the primary factor. It appears from these few cases that the change from Trendelenburg to horizontal position may play a role in this postoperative hypotension and hypoxemia. Further study of this problem is being carried out at the present time.

SPINOCAINE

Four spinocaine anesthesias were observed. In three of these the blood O_2 saturation was maintained within the normal range throughout the operation. In the fourth case, that of a negro undergoing a right inguinal hernia repair, the blood O_2 showed a gradual 25% decrease in saturation. This diminution in blood O_2 occurred as the patient complained of a "heavy" feeling in his chest. A pain sensitivity test proved that the spinal had become effective above the nipple line. Therefore, embarrassment of the respiratory muscles was probably a contributing factor in causing the blood O_2 decrease.

SUMMARY AND CONCLUSIONS

1. The importance of determining the oxygen saturation of the blood during anesthesia is emphasized.
2. Blood oxygenation values fluctuate so rapidly and so widely that intermittent gas analysis determinations are inadequate.
3. The portable photoelectric oxyhemograph, which gives a continuous recording of arterial O_2 saturation by means of opposed red and green filtered photoelectric cells, radio amplification (1,000,000 times) and an ink tracing, has supplied reliable and consistent results throughout operative procedures up to 10 hours in duration under various anesthetic agents.
4. Records on patients receiving pentothal show:
   (a) considerable individual susceptibility.
   (b) the advantage of 100% O_2 inhalation over room air prior to and during the induction as well as the value of O_2 administration during the course of the anesthesia.
   (c) the decreasing tolerance to pentothal which prevents adequate blood oxygenation even though 100% O_2 is administered in prolonged procedures.
   (d) the importance of using at least a 60-40 N_2O — O_2 mixture as a supplement to pentothal anesthesia.
   (e) the necessity for the continuation of O_2 inhalation during the postoperative period, at least until the patient reacts, if anoxemia is to be avoided.
5. Patients receiving cyclopropane, ethylene-ether, a combination of these

or spinocaine as anesthetic agents have not shown decreasing tolerance or cumulative effects as far as could be determined from the oxyhemograph curves.

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Discussion.—Dr. Robert M. Janes, Toronto: Dr. Behrmann has presented most beautifully what we believe to be a most important subject. At a meeting of the American College of Surgeons in New York last year, my associate, Dr. Kergin, presented some work that we had been doing on this problem. Our attention was

directed to it originally when we found that in doing bilateral resections for bronchiectasis our survivals were not as good after we started to do the dissection instead of the tourniquet operation. The explanation was apparently obvious in that the second operation was much more prolonged. Our studies paralleled very closely those you have heard. Certainly the oxyhemograph seems to give records that correspond sufficiently closely with samples of blood taken from an aorta during operation. We believe many of the unexplained deaths, particularly those in thoracic and abdominothoracic operations, are related to periods of prolonged anoxemia. The clinical estimate is not sufficiently accurate to detect this anoxemia, and we have come to feel that this apparatus should be part of the routine equipment in every operating room where these prolonged and serious operations are being undertaken.

DR. ROY D. MCCLURE, Detroit (closing): Oliver Wendell Holmes created a very beautiful word—anesthesia. The word anesthetist soon followed, and now a much more cumbersome, seven-syllable word—anesthesiologist.

We know that anesthesia, with or without preoperative sedation, may produce severe anoxemia or anoxia or, vice versa, severe anoxia may produce some degree of anesthesia.

Ours is a far cry from the first Kramer machine that Hartman worked with 11 years ago, a machine with two photoelectric cells applied to dissected-out artery and vein, two galvanometers each reflecting a beam of light writing on strips of photographic film. We showed this apparatus one sweltering hot summer day to our long-time friend, Charles F. Kettering. Off came his coat and on hands and knees he explored the inside workings of this box. He came up with the statement that the feeble impulses through the photoelectric cells could be amplified in a different way to greatly simplify this process. We developed a one-color photoelectric cell which was attached to the web of the hand of the anesthetized patient in 1939. Today you have seen the result of invaluable improvements, thanks to Kettering.

Milliken, who died so tragically in the mountains of Tennessee last spring, further developed this principle so that a photoelectric cell could be placed on the ear of an aviator inside his helmet, and when the oxygen content of his blood decreased at high altitudes a red light would flash on the instrument panel of his plane.

We believe that this method is developing into great practical value in our operating rooms. A number of cases have been reported of patients, blue under anesthesia, who became "vegetables" (not for dining table use, however) as a result of cerebral anoxia. There are undoubtedly many who suffer some permanent mental deficiency after anoxia without the cause ever being recognized. I would like to cite one case of many that have come to my personal attention. A brilliant girl student at Ann Arbor returned for a weekend with her parents in Detroit, and had her dentist extract an impacted molar tooth under nitrous oxide anesthesia. Shortly afterward she noticed slight double vision, but paid little attention to it. On returning to college she lacked concentration, her grades became poor and she finally flunked out. In my own mind there is no doubt that this was the result of anoxia. At the end of the year she returned to the same dentist for extraction of the opposite molar and was told by him—"Never take nitrous oxide for you can't stand it. Last year you got blue, stopped breathing, and we had to give you artificial respiration."

Perhaps routine mental tests in the early days of anesthesia, before and after prolonged or even short anesthesia, would have revealed many such cases. Our previous work has emphasized the dangers of oversedation with barbiturates and with morphine.

Dr. Hartman and Dr. Behrmann had hoped to show on our slides today simultaneously with these curves the continuous recording of the blood pressure, but this will soon be published.

PENICILLIN THERAPY WITH PROLONGED INTERVAL DOSAGE SCHEDULES*

W. A. ALTEMEIER, M.D.
CINCINNATI, O.

THE DOSAGE SCHEDULES devised for the therapy with penicillin of susceptible surgical infections have been based upon the assumed necessity of maintaining a therapeutic concentration of this agent in the circulating blood and tissues. This assumption probably resulted from a transfer of previous experiences with the sulfonamides. The effectiveness of dosage schedules based upon this concept has been established without question,[1-4] but each method has had one or more objections which have made it undesirable. The continuous infusion of penicillin either intravenously or intramuscularly, was soon abandoned in favor of single injections at intervals of two to four hours because of the patient's discomfort and the amount of time and effort needed to insure its efficiency. In this way the rapid excretion of penicillin was offset by the injection of penicillin at short intervals, but the inconvenience to patient and physician and the impossibility of administering penicillin to anyone but a hospitalized patient stimulated a further search for more satisfactory methods. Three plans were devised to overcome these objections and to extend the usefulness of penicillin to ambulatory or unhospitalized patients: delayed absorption, delayed excretion, and oral administration.

Delayed absorption, with the maintenance of a prolonged level in the blood, has been accomplished in several ways. With preparations of penicillin in oil and beeswax[5] or suspensions of penicillin in oil and pectin,[6] the absorption of water soluble penicillin was delayed by beeswax or pectin. An effective blood level for 24 or more hours can be maintained in 70 to 80 per cent of the cases with daily injections of 300,000 units in oil and if the dose is increased to 400,000 units, the level will be satisfactory in almost all of the cases for 24 or more hours. It has also been possible to retard the absorption by the injection of insoluble salts of penicillin. Our preference among these at the moment is procaine penicillin[7] prepared for parenteral injection either in an oil base or aqueous solution. Both have certain advantages over the oil and beeswax preparations, including a lower incidence of pain and local reaction. Other salts of penicillin with a low water solubility and slow rate of absorption are those formed by the heavy metals such as bismuth, silver, and mercury.

Retarded excretion of penicillin has been produced by the oral administration of caronamide in doses of 3 Gm. every four hours for periods of 2 to 19 days.[9, 10] This may be used to either decrease the interval between injections of aqueous penicillin, to enhance the blood levels two to seven times, or to decrease the amount of penicillin necessary for therapy of a given case. Two of its disadvantages are the large daily doses required and the nausea produced in some instances.

The oral administration of penicillin has been used effectively in selected cases providing it was buffered and its dose was five times greater than that of the necessary parenteral dose.[3] The ingestion of 100,000 units of buffered

* Read before the American Surgical Association, Quebec, Canada, May 28, 1948.

penicillin at intervals of four to six hours can usually be depended upon to produce and maintain a satisfactory concentration in the blood, and in its scope of application, it has been particularly useful in the therapy of ambulatory patients.

TABLE I.—*Clinical Results with Eight-Hour Penicillin Dosage Schedule*

Diagnosis	No. of Cases	Surgery	Results			
			Excellent	Good	Quest.	Failure
I. Staphylococcal Infections						
Cellulitis	20	4	13	7	..	..
Abscess	17	16	5	11	1	..
Infected wounds	15	4	5	9	1	..
Ulcer with cellulitis	5	..	5	3	1	..
Acute mastitis	3	..	..	1	2	..
Furunculosis	2	..	2	2	..	..
Parotitis	2	..	..	..	..	..
Carbuncle	2	..	2	2	..	..
Subacute osteomyelitis	2	..	..	2	..	..
Hydradenitis	1	..	1	..	..	..
II. Streptococcal Infections						
Cellulitis	8	1	6	1	1	..
Abscess	4	3	2	2	..	..
Infected wounds	4	..	2	1	..	1
Lymphangitis	2	..	2	..	..	..
Septicemia	2	..	1	..	..	1
III. Mixed Staphylococcal and Streptococcal Infections						
Ulceration and cellulitis	9	4	1	5	2	..
Abscess	9	6	3	7	..	..
Infected wounds	9	3	2	6	1	..
Cellulitis	4	2	2	..	2	..
Lymphangitis	2	..	2	..	..	..
Pleural empyema	2	2	..	2	..	..
IV. Pneumococcal Infections						
Postoperative pneumonia	6	..	3	2	1	..
Septicemia	1	..	1	..	..	..
V. Mixed Infections						
Peritonitis	12	12	..	5	6	1
PO wound infections	4	2	3	..	1	..
Acute cholecystitis	4	4	..	2	2	..
Deep abscess of neck	3	3	2	1	..	..
Intra-abdominal abscess	3	2	..	..	3	..
Acute salpingitis	3	1	..	2	1	..

It is well established, therefore, that the administration of adequate amounts of penicillin by any dosage schedule which maintains a more or less constant concentration of the agent in the blood will produce efficient chemotherapy. However, the necessity of maintaining a therapeutic concentration in the blood for successful treatment has not been proved, and evidence is accumulating that the bacteriostatic effect of penicillin persists for a considerable length of time after its disappearance from the blood. As early as 1944, the results of Tillet, et al,[11] suggested that penicillin inhibited the growth of invasive pneumococci for a considerable period after blood concentrations were no longer measurable. When injections were made at intervals of 12 to 16 hours, the results seemed to be just as satisfactory as those obtained when more frequent injections were used to maintain a therapeutic concentration throughout. Similar inhibitory effects on streptococci infecting mice for eight or more hours were suggested by the studies of Jawetz[12] in 1946. The studies of Zubrod[13] also indicated that the interval between doses on an aqueous solution of peni-

cillin could be greatly increased beyond four hours in the management of hemolytic Streptococcic infections in mice. More recently Marshall,[14] after discussing the discrepancies in methods of chemotherapy with penicillin and indicating his belief that the maintenance of a more or less constant blood concentration was unnecessary for efficient treatment in the human, advocated carefully controlled clinical trials to evaluate the efficiency of three, two, or even one injection per day in human infections. Preliminary studies of this nature at the Cincinnati General Hospital were reported shortly thereafter.[15, 16]

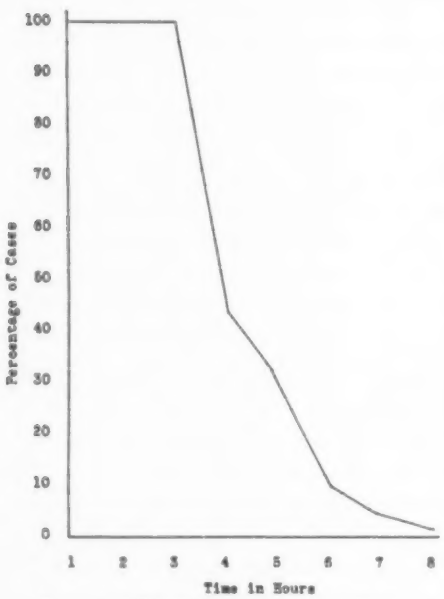

FIG. 1.—Showing the percentage of cases maintaining a concentration of .03 units of penicillin or more per c.c. of plasma 1 to 8 hours after a single intramuscular injection of 100,000 units of penicillin in aqueous solution.

MATERIAL AND METHODS

The current acute shortage of nursing personnel has stimulated us to explore the clinical effectiveness of the simple injection intramuscularly of larger doses of penicillin in aqueous solution every 8 to 12 hours. During the past eight months, we have treated 161 selected cases of established surgical infections at the Cincinnati General and neighboring hospitals. Externally located infections of moderate severity and known etiology were chosen for study in the majority of instances and most of them were produced by the hemolytic *Staphylococcus aureus* and/or the hemolytic Streptococcus. (Table I.)

Each of the cases was treated with either 100,000 units of penicillin at intervals of eight hours or 150,000-200,000 units at intervals of 12 hours. The penicillin was dissolved in sterile physiologic saline and injected intramuscularly using a volume of 1 cc. per 100,000 units. Determinations of the blood levels were made at intervals of one hour in 68 of the patients to determine the concentration of penicillin produced by one intramuscular injection. Whenever possible, the infecting bacteria were identified at the start of penicillin therapy and their susceptibility to penicillin determined in vitro. Studies were also made to determine the degree and duration of any inhibitory effect of a single application of two units of penicillin per cc. on the growth in vitro of five strains of the hemolytic *Staphylococcus aureus*, the hemolytic Streptococcus, the non-hemolytic Staphylococcus, and the non-hemolytic Streptococcus.

RESULTS

Measurements of Penicillin the Blood. Considerable variation in the levels produced by a single intramuscular injection of 100,000 units of penicillin

was obtained in 68 cases. Concentrations in excess of .03 units per cc. were maintained for at least three hours in 100 per cent of the cases, for four hours in 43 per cent, for 5 hours in 31 per cent, for six hours in 7 per cent, and for seven hours in 4 per cent. (Fig. 1.) Thus, an adequate level of penicillin was maintained through the eight hours in only 1.4 per cent of the cases. The two extremes of variation encountered in the levels of penicillin produced by a single injection of 100,000 units intramuscularly are illustrated in Figure 2.

Lag in Bacterial Growth Following Temporary Exposure to Penicillin. When five strains of the hemolytic *Staphylococcus aureus* which had been isolated from established human infections were exposed for two to four hours

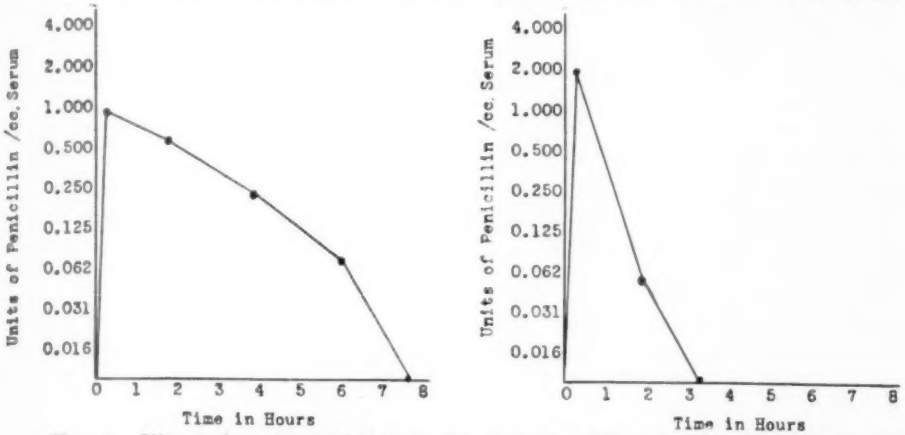

FIG. 2.—Illustrating the variation in blood levels obtained following a single injection of 100,000 units of penicillin in aqueous solution intramuscularly.

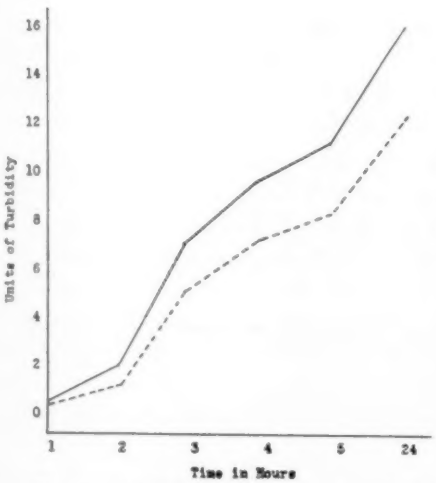

FIG. 3.—Illustrating the lag in growth of hemolytic Straphylococcus aureus produced by 2 hour exposure to 2 units of penicillin per c.c.
——— No exposure to penicillin
- - - - - Two hour exposure to penicillin

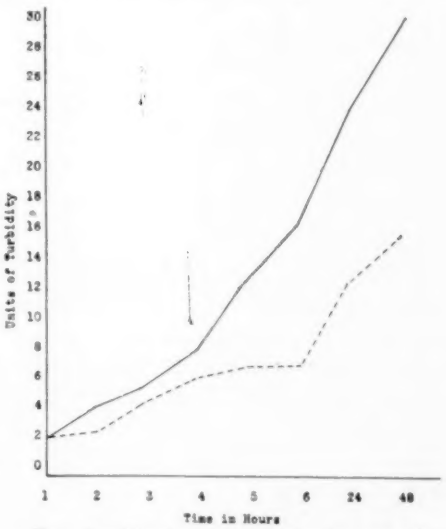

FIG. 4.—Illustrating the lag in growth of the hemolytic Streptococcus following a 4 hour exposure to 2 units of penicillin per c.c.
——— No exposure to penicillin
- - - - - Four hour exposure to penicillin

to the effect of two units of penicillin per cc. of media, a definite lag in their growth persisted for 8 to 24 hours after penicillin was removed and the organism reinoculated into fresh media without the chemotherapeutic agent. (Fig. 3.) Similar but less striking results were obtained with strains of the hemolytic

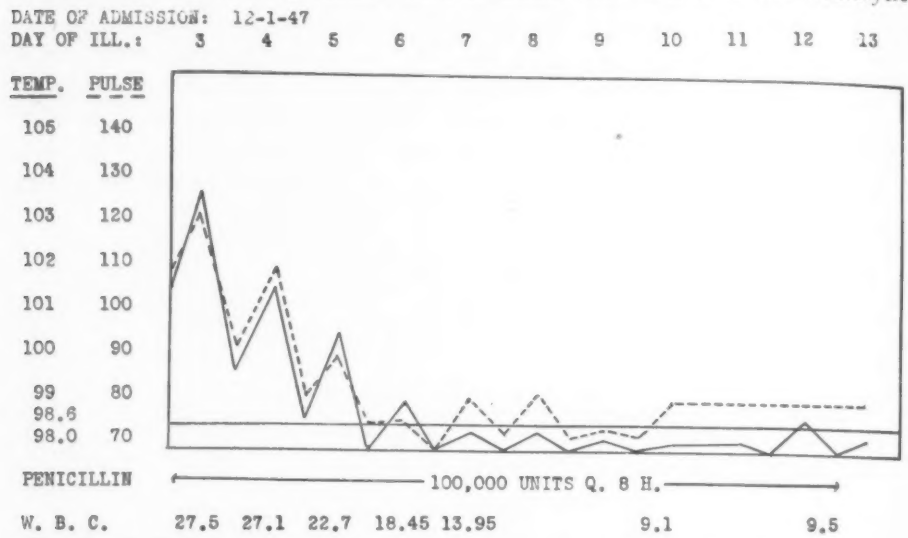

FIG. 5.—G. S. Infected laceration of right arm with cellulitis, lymphangitis, and lymphadenitis in a 38 year old colored female.

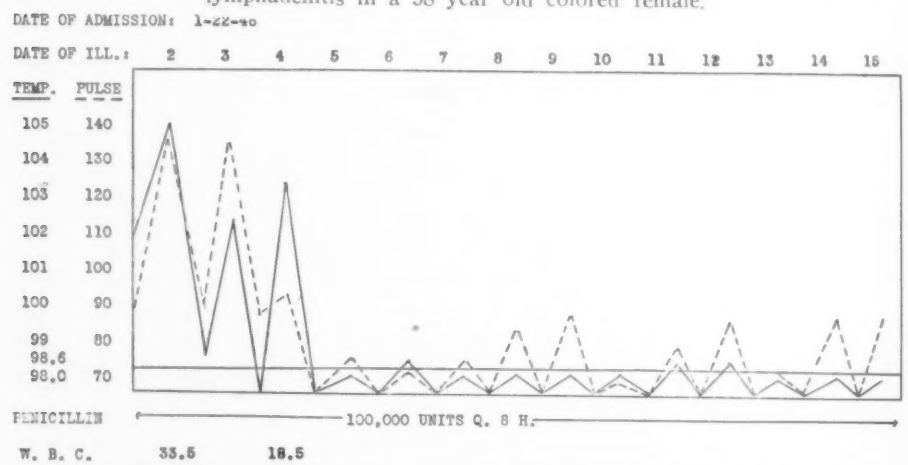

FIG. 6.—B. H. Age 25. Excellent response with complete control and spontaneous resolution of an acute interstitial mastitis of left breast following chemothtrapy with 100,000 units of penicillin every 8 hours.

Streptococcus (Fig. 4), the non-hemolytic Streptococcus, and the non-hemolytic Staphylococcus.

Clinical Results. The clinical results obtained in this series of selected cases were very gratifying and probably indistinguishable from those anticipated with the three or four hourly injections of penicillin with two possible exceptions of severe and extensive infections caused by the hemolytic Streptococcus in which penicillin therapy first with 100,000 units every eight hours

and later every three hours failed to save the patient's life. An arbitrary classification of the clinical results obtained with this dosage schedule is given in Table I. A satisfactory result was obtained in the great majority of the Staphylococcal infections treated and the pattern of response was the same which we have learned to expect with a lag of 24-72 hours preceding any obvious clinical change, spontaneous resolution of the earlier cases, and control of the invasive characteristics and localization in the later cases. (Figures 5, 6.) The Streptococcal infections were generally more severe than the other types, but satisfactory chemotherapeutic results were obtained in 17 of the 20 cases. The two failures occurred in fulminating and extensive infections produced by the hemolytic Streptococcus. In the mixed infections produced by both gram positive and gram negative bacteria, the incidence of satisfactory results was only 50 per cent as could be anticipated.

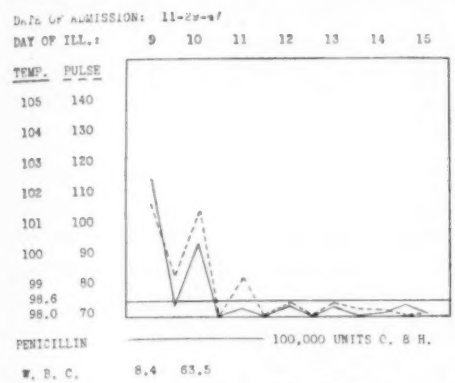

FIG. 7.—J. K. Age 14. Post traumatic ulcer of the leg with extensive cellulitis and lymphangitis produced by a hemolytic Streptococcus.

Serial Measurements of Bacterial Sensitivity. In only one case was evidence detected of a susceptible hemolytic *Staphylococcus aureus* developing definite resistance to penicillin during therapy with this schedule.

DISCUSSION

Experimental and clinical evidence indicates that the antibacterial effect of penicillin persists for some unknown reason for a considerable length of time after its disappearance from the circulating blood. Although this is a relatively small series of cases from which to draw any conclusions, it appears that the maintenance of a more or less constant blood level is probably unnecessary for efficient therapy in the human being. In our limited clinical experience, it appears that the intramuscular injection of an aqueous solution of penicillin containing 100,000-200,000 units every eight to 12 hours is an efficient and effective method of chemotherapy in susceptible infections of moderate severity. The method overcomes the disadvantages and inconveniences of the two- to four-hour dosage schedule to a large extent and has not resulted in any increased tendency of the bacteria to develop resistence of penicillin. The administration of only two or three injections per 24 hours decreases the task of the nurse and releases part of her time for other more necessary nursing duties.

In addition to the lessened discomfort and inconvenience of the patient, the method is of great practical importance at the moment because of the nursing shortage throughout the nation. The eight- and 12-hour dosage schedule is advocated at present only in susceptible infections of moderate severity or less until further experimental information is gathered.

THE RESULTS OF THE SYSTEMIC ADMINISTRATION OF THE ANTIOBIOTIC, BACITRACIN, IN SURGICAL INFECTIONS. A PRELIMINARY REPORT*

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BACITRACIN IS AN ANTIBIOTIC produced by the Tracey strain of *Bacillus subtilis*. It was isolated from the mixture of organisms found in the debrided tissues removed from a compound fracture of the tibia, while studying the prevention of infection in contaminated wounds by the use of sulfonamides.[1] Its commercial production has met with some difficulties similar to those encountered during the development of both penicillin and streptomycin.

During the early stages of the process of purification, bacitracin was used in the local treatment of various types of surgical infections and the first 100 cases were reported in March, 1947.[2] It yielded favorable results comparable to penicillin, and in many cases in which penicillin had failed. It was then taken up by the dermatologists, Miller and Slatkin, who reported success in the treatment of various types of pyodermias.[3] Similar encouraging reports were made in the field of ophthalmologic infections.[4]

During the past 20 months, purification and standardization have reached a point which has permitted the systemaic use of bacitracin. A number of groups are trying to evaluate this antibiotic in the systemic treatment of pneumonia, syphilis and various types of surgical infections. These studies are being carried out with the aid of funds provided by the Medical Research and Development Board of the Surgeon General's Office and the Antibiotics Study Section of the National Institute of Health. The leaders of these groups are co-authors in the presentation of this report.

The Surgeon General's Office called upon the Food and Drug Administration to set up specifications and tentative standards for bacitracin which would permit its systemic use under experimental conditions and which would safeguard the patients during the course of its clinical appraisal. Therefore, on January 20th of this year, Dr. Henry Welch called the manufacturers together and they subsequently agreed upon provisional specificiations regarding potency, solubility, stability, toxicity for mice, pyrogenic effects for rabbits, and vasopressor and vasodepressor effects on dogs. These minimum specifications must be met by all of the manufactured preparations before they can be applied in the treatment of human infections.

Bacitracin has a wide antibacterial spectrum, being effective against most strains of hemolytic streptococci, nonhemolytic streptococci, coagulase-

* Read before the American Surgical Association in Quebec, Canada, May 28, 1948.

positive staphylococci, pneumococci, gonococci, anerobic cocci in general, all of the gas gangrene group of organisms and the bacillus of tetanus, the diphtheria bacillus and diphtheroids, the spirochetes of syphilis and mouth spirochetes, the actinomycotic group of organisms, and among the protozoans, the Endamoeba histolytica. There is little or no action against the large group of aerobic Gram negative non-spore forming bacilli.

The chief advantages that bacitracin has over penicillin are (1) that it is not inhibited by the organisms which produce penicillinase and is, therefore, more likely to be effective in infections due to bacterial mixtures. (2) It is more slowly eliminated from the body and, therefore, can be given at longer intervals. (3) Its effectiveness against bacteria is in direct proportion to its concentration.[5] This has been brought out by Eagle in comparing the lethal action of penicillin and bacitracin against the spirochetes of syphilis. He has also demonstrated a significant synergistic action between penicillin and bacitracin in the treatment of experimental syphilis whereby small fractions of therapeutic doses of each, when combined, yield a therapeutic result.[6] (4) So far, bacitracin has shown less tendency to produce allergic or hypersensitive reactions but these may come with its more extended use. Certain strains of bacteria gradually build up a resistance to bacitracin but this is of a low order. As time goes on, more and more organisms belonging to groups susceptible to penicillin are proving to be resistant to it and in many instances these organisms are susceptible to bacitracin.

Its chief disadvantage, as compared with penicillin, is that it has not yet been obtained in a pure or crystalline form and, in the present state of its impurity, it produces, when injected systemically in man, certain evidence of nephrotoxicity which limits its dosage and the duration of treatment. This will be discussed more fully below.

Its chief advantages over streptomycin are its wider antibacterial spectrum, particularly with regard to the anaerobic organisms, and the low order of the development of resistance during the course of treatment. Its chief disadvantage with respect to streptomycin is its ineffectiveness against the Gram negative aerobic non-spore forming bacilli.

While bacitracin is not inactivated by gastric acidity or by the proteolytic ferments of the gastro-intestinal tract, it is not absorbed to any extent from the alimentary canal. However, while it cannot be given systemically as a mouth medication, it remains active and effective against the susceptible groups of intestinal organisms, particularly the *Clostridium welchii* and the intestinal streptococci, and it can be recovered from the feces in a concentration well above the lethal level for these organisms. It may, therefore, be combined with streptomycin or some of the relatively insoluble sulfonamides to minimize the activity of the intestinal flora before surgical procedures on the bowel. It has also been found effective in a few cases of intestinal infections, namely, in chronic ulcerative colitis

and regional ileitis. Furthermore, encouraging results are being obtained by mouth administration in both the acute and chronic stages of amebic dysentery.

The present report includes 105 cases of surgical infections observed in the units set up for the appraisal of bacitracin in New York, Cincinnati, New Orleans, San Antonio and Philadelphia. These studies are being carried on in a uniform manner and comparable data are being obtained in all cases. These data are being recorded on summary sheets especially prepared for this study, designed to bring out the essential features of these cases. In the course of the coming year, it is hoped that records will be obtained on approximately 1000 cases. Plans are going forward to analyze the results and determine their statistical significance so that at the end of that time, we may have a clearly defined knowledge of the indications for and limitations of this new antibiotic. These data will be collected and analyzed at the unit in New York.

The information which is being gathered with regard to various types of surgical infections includes diagnosis and duration (30 days having been set as the dividing line between acute and chronic infections); a record of the previous treatment, if any, both local and systemic; the general status of the patient as indicated by the blood count, sedimentation rate and kidney function, including the tests for nonprotein nitrogen or blood urea nitrogen, the clearance of phenolsulfonephthalein, and the presence of albumin, sugar, casts and cellular elements; the dosage of bacitracin, both systemic and local; the symptoms and signs of infection before and during treatment; the time relationship of any surgical procedure; the blood levels; the per cent of bacitracin excreted in the urine; a complete bacteriologic analysis of the infection before, during and after treatment and the results obtained.

It is understandable, since the advent of the sulfonamides and the antibiotics, particularly with the ready availability of penicillin and its low toxicity, that patients coming to any hospital with an infection are likely to have had some form of antibacterial therapy either self-administered or prescribed by the family doctor. This means that today relatively few patients are available for primary treatment with a new form of therapy. This is a handicap to the success of the new agent because it not only increases the proportion of cases which are resistant to all treatment but prolongs the duration of the illness before the institution of the new form of treatment. Until confidence can be built up in a new drug, doctors are not warranted in using it in the primary treatment of an infection. In view of these facts, the authors of this paper recognize that bacitracin will not be of any practical importance unless it can succeed where other forms of treatment have failed or unless it can demonstrate its clear-cut superiority over other forms of treatment so that it becomes the treatment of choice. As time goes on, however, if bacitracin demonstrates its effectiveness and

its safety and if the cases in which it is used are carefully studied and the indications for and the limitations of this treatment can be clearly defined, then it may be that certain conditions will indicate its use as the initial treatment.

During the preliminary stages of this investigation, the leaders of each group have proceeded cautiously with relatively small doses and a large proportion of the cases herewith reported include those which have failed to respond to other forms of treatment. Any statistical analysis of the results of such treatment must keep this in mind. It is exceedingly difficult to run parallel series of cases and to compare different forms of treatment with one another and, in any study of established infections, the controls must lie in the cases themselves and their response to previous forms of treatment.

Bacitracin has been used systemically in steadily increasing number of cases for the past year and a half. This number has been limited chiefly by production difficulties in obtaining a uniform product of consistent potency and low toxicity. More than 100 cases of syphilis have been treated by Eagle and his associates with bacitracin or a combination of bacitracin and penicillin. Reisner has treated over 25 cases of pneumonia. These will be reported elsewhere. A few other so called medical infections, such as malignant endocarditis, have been treated and others are being studied. This paper covers all of the cases of surgical infections so far treated systemically in the units set up especially for the appraisal of bacitracin and comprises 105 cases, the results of which are shown in the accompanying Table I.

TABLE I.—*Results Obtained in* 105 *Cases of Surgical Infections Treated by the Systemic Administration of Bacitracin*

DIAGNOSIS	Total Cases	RESULTS OF TREATMENT			
		Excellent	Good	Questionable	No Effect
Cellulitis	17	6	9	0	2
Deep abscess	15	0	10	2	3
Infected accidental wound	13	6	4	1	2
Chronic osteomyelitis	7	0	6	1	0
Operative wound infection	4	1	1	1	1
Multiple furuncles	4	0	2	1	1
Synergistic gangrene	3	3	0	0	0
Simple ulcer of skin	3	0	2	1	0
Ulcerative colitis	3	0	2	1	0
Thrombophlebitis	3	0	0	3	0
Brain abscess	3	0	0	0	3
Acute osteomyelitis	2	0	1	0	1
Undermining burrowing ulcer	2	0	2	0	0
Actinomycosis	2	0	1	1	0
Infected compound fracture	2	0	1	0	1
Meningitis	2	2	0	0	0
Human bite infection	2	2	0	0	0
Regional ileitis	2	0	2	0	0
Carbuncle	2	0	2	0	0
Miscellaneous*	14	2	5	3	4
TOTALS	105	22	50	15	18

Favorable results in 69% of cases.

* Includes one case each of septic abortion, breast abscess, calciled abscess, decubital ulcer, mediastinitis, acute suppurative tenosynovitis, bronchiectasis, cholangiitis, tuberculosis of glands of neck, strangulated hernia, pelvic thrombophlebitis, intestinal obstruction, ulcers of perineum and scrotum, tetanus with gangrene of foot.

The results of treatment are classified into four groups. They are called 'Excellent' if infection subsided rapidly and dramatically within 72 hours. They are called 'Good' if there was a definite response to the drug but the effect was more gradual during the course of a week or ten days. The benefit is 'Questionable' if the case might have done just as well without the drug, and the result is labeled 'No Effect' if the infection went on its course regardless of drug treatment.

The results which are called either 'Excellent' or 'Good' may be considered together as favorable results and the other two categories as unfavorable results, although, in the 'Questionable' group, there may be some cases in which the drug was of value. However, in order not to seem too optimistic, the doubtful cases are not put to the credit of bacitracin.

It will be seen that only three diagnostic groups include more than ten cases and the results in the smaller groups are not of statistical significance nor necessarily representative of what might be expected in those conditions. If we take the group as a whole, we find that the results were favorable in 69 per cent of the cases, whereas in the three categories having the largest number and almost one-half of the cases the results were favorable in 78 per cent. In the miscellaneous group including one case of each diagnosis, favorable results were obtained in only 50 per cent of the cases.

It is of interest that in three groups all of the results were 'Excellent,' namely, synergistic gangrene, meningitis, and human bite infection. These meningitis cases were associated with surgical conditions and, while this disease is not ordinarily considered a surgical infection, they are included in this report. It has been found that bacitracin does not penetrate well into the spinal fluid, only reaching a tenth of the level found in the blood [7] but in the presence of infection this penetration is increased.[8] However, if local application can be made by intrathecal injection or topical application, it is effective against susceptible organisms if it can reach the area involved, and it is not locally injurious to the meninges. In the cases of synergistic gangrene, these results are particularly significant because in every case this painful destructive process had spread over a large area of the body surface over a period of months, unchecked by many different forms of treatment including the sulfonamides and penicillin and in each instance the process came to a sudden halt within 72 hours, the necrotic skin was automatically loosened and subsequently separated from the necrobiotic zone, and the areas became covered with epithelium spontaneously without the necessity for any surgical procedure, even skin grafting. It will be remembered that this rare but distressing condition formerly required wide excision in order to effect a cure. Human bite infections may be particularly amenable to bacitracin therapy if given before extensive destruction of tissue has occurred because of the striking susceptibility of anaerobic streptococci and spirochetes.

The highest percentage of favorable results, 88 per cent, was obtained in the cases of cellulitis. This might be expected because organisms causing

these diffuse lesions are usually susceptible to bacitracin and because patent blood vessels permit the infiltration of any medication into the zone of infection. Furthermore the alarming nature of such a case often brings the patient to the doctor in the early stages of the disease.

It is perhaps of equal interest from a scientific point of view to point out those two groups in which the results were unfavorable, namely, throm-

FIG. 1. FIG. 2.

FIG. 1.—Patient O.S.: Cellulitis of arm of four months' duration with seven sinus openings, two incisional and five spontaneous, before bacitracin treatment.

FIG. 2.—Patient O.C.: One month after bacitracin treatment. Sinuses all healed and surgery obviated.

bophlebitis and brain abscess. In the former group, the element of infection is probably secondary to physical and chemical changes in the blood, while in the cases of brain abscess there are other factors prejudicial to success which will be discussed later.

Although they were few in number, the encouraging results obtained in ulcerative colitis and regional ileitis suggest a thorough investigation of the value of bacitracin in these fields because of the fact that it may be administered by mouth for its local action on the bowel as well as systemically by muscular injection. Like streptomycin, as we have mentioned above, bacitracin is not absorbed to any extent from the alimentary tract, and comes through in the stool in a concentration well above the lethal level for susceptible organisms such as the streptococci and clostridia. Although the

causes of these diseases are not known, infection is of major importance and may be either primary or secondary.

In studying the results obtained in these cases, it seems to the authors to be particularly worthwhile to analyze the two extremes, namely, those yielding prompt, dramatic, almost immediate response to the drug treatment and those in which there is patently or obviously no effect whatsoever. In the

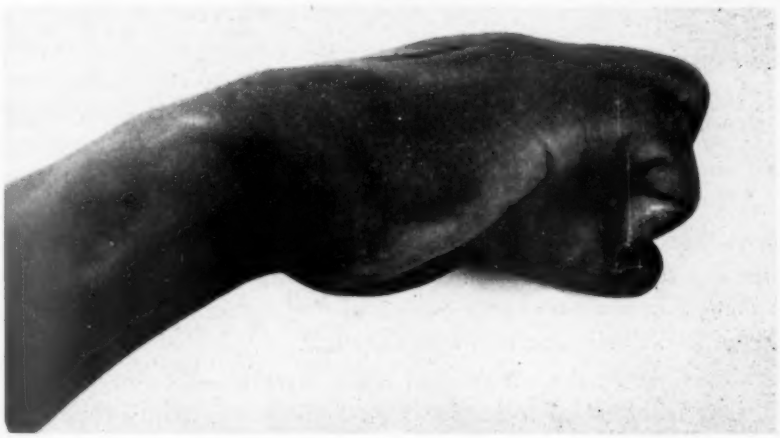
FIG. 3.—Patient E.W.: Actinomycosis of hand eleven months after human bite, before bacitracin treatment

'Excellent' group, there are 22 cases, three of which, namely, the synergistic gangrenes, have already been referred to. The two largest groups are those of cellulitis and infected accidental wounds. Cellulitis is one of the characteristic manifestations of hemolytic streptococcal infections and the more virulent strains of hemolytic *Staphylococcus aureus*. The hemolytic streptococci are particularly susceptible to bacitracin but they are also susceptible to the sulfonamides and penicillin. However, for one reason or another a number of these cases had not responded to these other agents and we find, in studying the bacteriology of these 'Excellent' results, that more than half yielded on culture streptococci, either hemolytic, nonhemolytic, microaerophilic or anaerobic varieties which seemed to play a dominant role in the infection. We also find among these cases four in which a hemolytic *Staphylococcus aureus* was the principal organism and proved to be resistant to penicillin but susceptible to bacitracin. In one case in which there was a combination of hemolytic streptococcus and hemolytic *Staphylococcus aureus*, it was found that both of these organisms were susceptible to both penicillin

and bacitracin and, although 2,100,000 units of penicillin within 24 hours failed to stop the infection, it responded within another 24 hours to 20,000 units of bacitracin given every six hours.

There were 18 cases in the group in which bacitracin had no effect on the course of the infection. One of these was a post-hysterectomy pelvic cellulitis with necrosis of the vaginal vault which had failed to respond to

A



B

FIG. 4A.—Patient E.W.: Two months after bacitracin treatment and surgical excision. Full extension of fingers. B.—Patient E.W.: Two months after bacitracin treatment and surgical excision. Full flexion of fingers.

the sulfonamides, penicillin and streptomycin, and the patient was practically moribund when bacitracin was called for. Another case was a little girl of three who died from intestinal obstruction. This was caused by an abscess arising from a perforation of the tip of the appendix which was over on the left side and which surrounded and obstructed the sigmoid. Three patients with brain abscesses died without benefit of surgical drainage, bacitracin as well as the sulfonamides and penicillin having failed to reach the focus in sterilizing concentration. In the other cases, the causative organisms were resistant to bacitracin. Two of these were staphylococci which were susceptible to penicillin and these patients responded to later treatment with penicillin. The other cases had a multiplicity of organisms, one with four, one with seven and one with nine different species, the majority of which were resistant to bacitracin.

FIG. 5.—Patient V.H.: Osteomyelitis of stump of femur three years after receipt of battle wound, with two draining sinuses and three sequestra, before bacitracin treatment.

When bacitracin was first discovered, we were not only impressed with the wide range of its antibacterial action but we were particularly happy to find that it appeared to have no toxicity for laboratory animals and gave no evidence of local irritation at the site of injection when surgical infections were so treated. In order to get away from extraneous factors and to develop a uniform product, we utilized a synthetic medium which yielded from 6 to 12 units of bacitracin per cc. at the peak of production on the third day of incubation. The concentrated antibiotic obtained from this medium showed no evidence of toxicity on repeated and prolonged periods of injection in our laboratory animals.

However, when the commercial firms were asked to prepare this antibiotic, they laid particular emphasis on finding a medium in which it could be produced in high titer. This was found in a medium made from soy bean flour which was cheap and easy to prepare and which yielded five to ten times as many units per cc. as the synthetic medium. When that product was sent to us for clinical and experimental study, we began to see evidences of

toxicity, most important of which in human cases seemed to be the development of traces of albuminuria and occasionally nausea and vomiting. A careful study of this material by Scudi and his associates [7, 9, 10] demonstrated some nephrotoxicity for mice and to a lesser degree for monkeys but none

FIG. 6.—Patient V.H.: One month after excision of necrotic bone and removal of sequestra, with wound completely healed, after bacitracin treatment. Remaining foreign bodies in soft parts away from infected field.

at all for rabbits, rats and dogs. However, even in mice these kidney changes only occurred with very large doses well above the corresponding contemplated doses for man. Cautious use in human infections, produced a slight degree of albuminuria regularly, and occasionally abnormal cells and granular casts appeared in the urine, but we were happy to note that these abnormal

signs were transient and often disappeared during the course of treatment and that there was no appreciable rise in the nonprotein nitrogen or in the blood urea nitrogen. It was also observed that, if there was a persistance of any abnormality, it disappeared promptly after the termination of treatment.

TABLE II.—*Renal Excretion of Bacitracin—Patient V. H.*

Date	Specimen	Total Ml	Units Per Ml	Total Units	Intake (000)	Per Cent Excreted	pH	Albumen	Casts
1/29	24 hrs. ...	2050	13	26,650	...	...	7	0	0
1/31	24 hrs. ...	2300	30	69,000	132	52.3	6.5	st	0
2/1	18 hrs. ...	1270	30	38,100	99	37	6	ht	few
2/2	6 hrs. ...	800	60	48,000	...	...	7	t	few
2/3	6 hrs. ...	650	30	31,500	...	...	7	0	rare
2/4	24 hrs. ...	1900	20	38,000	132	28.7	7	0	0
2/5	24 hrs. ...	2100	40	84,000	132	63.6	7	spt	0
2/6	24 hrs. ...	1500	..	....	...	...	6.5	0	0
2/7	24 hrs. ...	1800	54	97,200	120	81	6.5	0	0
2/8	24 hrs. ...	1500	60	90,000	120	75	6.5	0	0
2/9	24 hrs. ...	1500	60	90,000	120	75	7	0	0
2/10	24 hrs. ...	1650	23	37,950	120	31.6	7	0	0
2/11	24 hrs. ...	1900	44	83,600	120	69.6	7.5	0	0
2/12	24 hrs. ...	2750	44	121,000	120	100	7.5	0	0
2/13	24 hrs. ...	2400	29	69,600	120	58	6	0	0
2/14	24 hrs. ...	2000	24	48,000	120	40	6.5	0	0
2/15	24 hrs. ...	1900	42	79,800	120	66	7	0	0
2/16	24 hrs. ...	2200	40	88,000	120	73 3	6	0	0
2/17	24 hrs. ...	1800	33	59,400	120	49.5	7.5	0	0
2/18	24 hrs. ...	1500	39	58,500	120	48	6.5	0	0
2/19	24 hrs. ...	2100	22	42,000	120	35	7.5	0	0
2/20	24 hrs. ...	2400	24	57,600	120	48	7.5	0	0
2/21	24 hrs. ...	2630	32	84,160	120	70.1	6	spt	0
2/22	24 hrs. ...	980	44	43,120	120	36	7.5	0	0
2/24	24 hrs. ...	2150	46	98,900	120	82.4	7.5	0	0
2/25	24 hrs. ...	2050	54	110,700	120	92.2	7.5	0	0
2/26	24 hrs. ...	1400	24	33,600	120	28	7	st	0
2/27	24 hrs. ...	2300	31	71,300	120	59.4	7.5	0	0
2/28	24 hrs. ...	2000	52	104,000	120	86.6	7.5	0	0
2/29	24 hrs. ...	1800	33	59,400	120	50	7.5	0	0

spt—Smallest possible trace.
st—Slight trace.
t—Trace.
ht—Heavy trace.

TABLE III.—*Renal Excretion of Bacitracin—Patient J. L.*

Date	Specimen	Total Ml	Units Per Ml	Total Units	Intake (000)	Per Cent Excreted	pH	Albumen	Casts
2/16	Before ...	120	0	0	0	0	..	0	0
2/16	Dose 1 ...	170	21	3,570				spt	0
2/17	18 hrs. ...	600	37	22,200	80	27.75	6.5	st	rare
2/19	24 hrs. ...	1000	34	34,000	80	42.5	7	ht	occ.
2/20	24 hrs. ...	1300	34	44,200	80	55.2	5	ht	mod.
2/21	24 hrs. ...	1200	38	45,600	80	57	5	ht	mod.
2/22	24 hrs. ...	750	46	34,500	80	43.1	4.5	ht	occ.
2/24	24 hrs. ...	2050	40	82,000	80	102.5	4.5	ht	mod.
2/25	24 hrs. ...	995	54	53,730	80	67.1	4.5	ht	many
2/26	24 hrs. ...	1300	33	42,900	80	53.6	4.5	t	mod.
2/27	24 hrs. ...	1000	35	35,000	80	..	4.5	t	mod.
2/28	24 hrs. ...	1060	11	11,600	0	..	4.5	st	occ.
2/29	24 hrs. ...	1400	0	0	0	0	4.5	st	occ.
3/3	...	....	..	....	..	..	4.5	spt	0

spt—Smallest possible trace.
st—Slight trace.
t—Trace.
ht—Heavy trace.

This was the experience of all the units working with bacitracin and we began to have a sense of confidence in the safety of the drug, which we felt would permit effective clinical doses without any evidence of damage to the kidneys. Two illustrative cases are shown in the accompanying Tables II and III.

It was at this point that the Food and Drug Administration set up the temporary specifications of bacitracin, mentioned above, which were considered an adequate safeguard against injury to the patients.

About the first of the year, the methods of production and all of the material produced by surface growth in bottles by the Ben Venue Laboratories of Bedford, Ohio were taken over by the Commercial Solvents Corporation. The Ben Venue Laboratories had been furnishing us with our material and during the first two months of this year their stock-pile was gradually turned over to us by the Commercial Solvents Company in quantities as we needed it and it was used up on these patients. In February we

FIG. 7.—Patient A.W.: Bacterial synergistic gangrene of four months' duration, following hysterectomy, lesion involving lower half of abdomen and both thighs, before bacitracin treatment.

began to receive bacitracin made by the Commercial Solvents Corporation by the deep tank method, and then, for the first time, one of the units began to notice more pronounced evidences of nephrotoxicity than we had seen before with higher degrees of albuminuria and more cellular abnormalities, a higher rise in retained nitrogen and symptoms of lassitude on the part of the patient. Soon afterward these same results were observed in other units and in one case there was a temporary renal shut-down while in another there was an irreversible rise in blood urea nitrogen.

The case with the renal shut-down occurred in a patient with an extensive and rapidly spreading cellulitis of the neck which had not responded to penicillin. The causative organism was not obtained but the clinical activity of the organism indicated a hemolytic streptococcus. He was given double the usual primary dose of bacitracin and this was administered every four hours for the first 24 hours. The infection promptly came under control so that it is listed among the 'Excellent' results. However, after the cessation of treatment and after the patient returned home, he noticed a decrease in

the output of urine and a general lassitude which brought him back to the clinic. Here it was found that he had albumin in the urine and a rise in blood urea nitrogen and therefore he was admitted to the hospital for study. Gradually his urinary output rose to normal although the specific gravity remained low. His blood urea nitrogen came down to normal levels.

The toxicity of the presently available commercial product is under very close study. There are a number of facts which indicate that the toxic factors

FIG. 8.—Patient A.W.: Synergistic gangrene wound completely epithelialized, seven weeks after starting bacitracin.

are by-products of manufacture, particularly of the deep tank method, and they appear in certain batches of the preparation but not in all. It is hoped and expected that they will be eliminated in the near future.

The exact chemical nature of bacitracin has not yet been determined although studies are being pursued in this direction in several different laboratories. We know that it is made up of a number of amino acids although it does not have the properties of a pure polypeptid. Some of these amino acids may be unnatural and thus give rise to nephrotoxicity, as is known to be the case with d-serine. It may be possible to eliminate these unnatural amino

acids without interfering with the antibiotic effect or it may be possible to neutralize their nephrotoxic action by some chemical means. For example, it has been demonstrated that a number of salts can greatly reduce the toxic action, among these are sodium chloride, sodium bicarbonate and sodium sulfate. In the administration of the antibiotic, therefore, for the time being

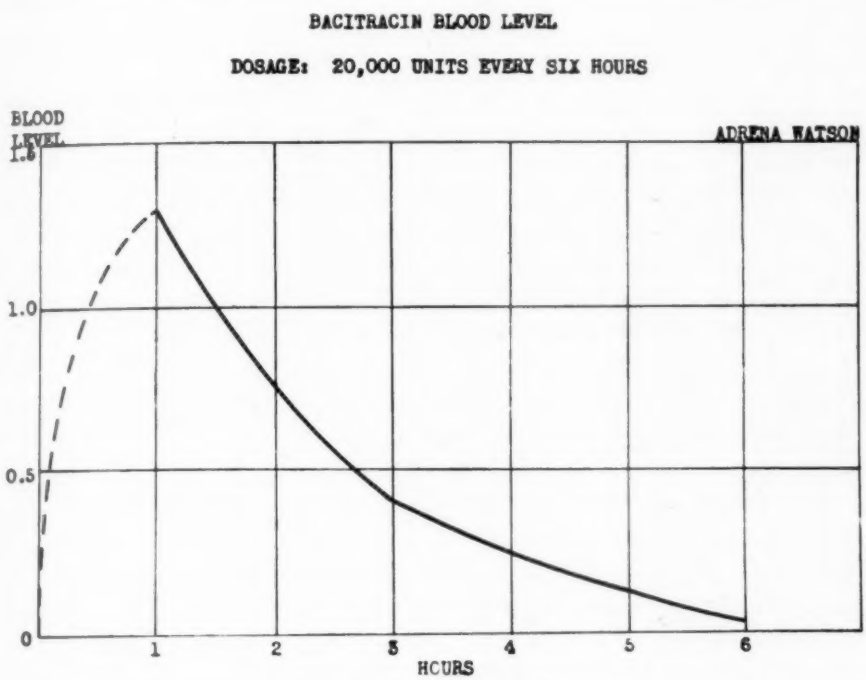


FIG. 9.—Patient A.W.: Bacitracin blood level after intramuscular injection of 20,000 Units.

the solvent should contain one or another of these salts. It is the present practice to dissolve the lyophilized product in 2 per cent novocaine made up in normal saline, and to alkalinize the patient so that the urine is always at a pH of 6 or more.

It is well known that individual animals and certainly individual human beings vary considerably in their reaction to all of these antibiotics and some persons may have an idiosyncrasy to them or develop an allergy to them. So far, these reactions have been minimal with bacitracin.

SUMMARY

1. The new antibiotic bacitracin may be used systemically as well as locally in the treatment of surgical infections.

2. Specifications have been set up by the Food and Drugs Administration to safeguard its use in clinical cases.

3. The results in 105 cases of surgical infections treated by the systemic

administration of the new antibiotic have been presented. These represent a wide diversity of conditions but for the most part they were cases which had failed to respond to the sulfonamides and to the other antibiotics.

4. There was an overall favorable response in about 70 per cent of these cases and, in about one-fifth of these, the results were dramatic.

5. Of particular interest were three cases of extensive progressive bacterial synergistic gangrene, all of whom responded within 72 hours and recovered without the necessity for surgical excision.

6. In the three largest groups, namely, "cellulitis", "deep abscess" and "infected accidental wound", favorable results were obtained in 78 per cent of the cases.

7. In the dramatic group, the causative organisms were for the most part in the staphylococcal and streptococcal groups. In the latter classification, were found hemolytic, nonhemolytic, microaerophilic and anaerobic streptococci. In a considerable number of staphylococcal strains, we found a resistance to penicillin and a susceptibility to bacitracin.

8. In 14 per cent the results were questionable and in a slightly higher percentage, the results were frankly nil. In most of these cases the causative organisms were resistant to bacitracin.

9. In the majority of the patients in the whole series there was a transient albuminuria which disappeared either during continued treatment or soon after treatment was discontinued.

10. Some of the later preparations of bacitracin made by the deep tank method have shown evidence of nephrotoxicity. New specifications will have to be drawn up to detect these toxic factors. When the presently available bacitracin is used systemically, there should be repeated tests of kidney function pathology and treatment should be discontinued if there is any indication of serious damage.

11. However, with doses which are not damaging to the kidneys, favorable and sometimes dramatic results may be expected in surgical infections caused by organisms which are susceptible to bacitracin. This covers a wide range of bacteria which are commonly found in surgical infections.

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DISCUSSION.—DR. E. P. LEHMAN, Charlottesville, Va.: I want to report briefly on some work with bacitracin that is being carried on in our laboratories by Dr. William R. Sandusky under the guidance of Dr. Meleney. This work is concerned with the use of bacitracin in experimental clostriadial infections. The experiments were performed by exposing muscle in guinea pigs, crushing it, and closing the wound. After the would was closed, varying amounts of Clostridium Welchii were injected into the area of damaged muscle and a number of the animals were treated with varying doses of bacitracin.

There were 44 control animals, of which only 17 survived. I want to point out that 26 animals died of gas gangrene with the usual picture of an enormously swollen leg and the other phenomena with which we are all familiar. One died of other causes. In the 93 animals treated with bacitracin, none died of *C. Welchii* infection. There were 25 deaths from other causes—pneumonia, persistent diarrhea, and in one or two instances intestinal obstruction as the result of intussusception. The number surviving was 68. Counting in the deaths from other causes the mortality rate is 59 per cent in the controls and 27 per cent in the bacitracin treated animals, which presents a statistically significant difference. In those animals that died of other causes there was no evidence of *C. Welchii* infection at autopsy. Leaving out the animals that died of other causes, there is no mortality in the bacitracin treated series and a mortality of 59 per cent in the animals that had no bacitracin.

At the time these experiments were done there was a good deal of disease in the guinea pig colony and it is not possible to say that this relatively large number of deaths in the experimental series had anything to do with the drug itself. The fact that they did not occur in the other series might suggest that it was a toxic factor in the drug, but I should like to hear Dr. Meleney's comment on that. The results in any event appear to suggest strongly that bacitracin has a specific effect in the prevention of clostridial infection in the guinea pig.

DR. I. S. RAVDIN, Philadelphia: I should like to review a few impressions we have obtained with the use of bacitracin in the project under Dr. Meleney that Dr. Zintel is heading in our clinic. The clinical results of systemic administration of bacitracin have been encouraging but there can be no doubt, as Dr. Meleney said, and Dr. Lockwood re-emphasized, that bacitracin is nephrotoxic for man. Dr. James Mitchie of our Section in Urology has been studying the possibilities of renal injury with this substance. Four patients have been extensively studied for evidence of renal, hepatic and blood cytology toxicity and have uniformly shown moderately severe renal tubular injury.

One patient who received 3,744,000 units of bacitracin over a period of 13 days had a 66 per cent reduction in tubular function; one month later the tubular function was still 22 per cent below the premedication value. A second patient receiving 200,000 units of bacitracin daily for 10 days had an 85 per cent reduction in tubular function;

12 days after bacitracin was discontinued the tubular function was still 66 per cent below pre-medication value. The observations of Dr. Meleney and Miss Johnson, that the nephrotoxicity of the bacitracin preparation does not parallel the antibiotic potency does suggest, as he has said, that the nephrotoxic factor is not a part of the bacitracin molecule. Until improved methods of manufacture eliminate the nephrotoxic factor, we must move very cautiously in further systemic use of this substance, for there can be no doubt that the renal injury is not a short-lived one in many of these patients, but persists over a very considerable time.

Dr. Champ Lyons, New Orleans: Beginning rather cautiously a year ago when this problem was first presented to us, namely, that of deciding between bacitracin therapy for penicillin-resistant infections and the extension of other methods, we proposed to try combined therapy. We had already begun to vary the interval of dosage, and for the past eight months we have routinely used a dosage of penicillin every eight hours, as prescribed by Dr. Altemeier, with complete satisfaction to ourselves.

Instead of treating penicillin-resistant infections with bacitracin, we elected to use mixed thrapy, because the evidence in the literature suggests very strongly that any antibiotic of bacillary origin will have inseparably produced in that mixture some nephrotoxic constituents. Until that problem is solved we have decided not to use any antibiotics of bacillary origin. We have used mixtures of penicillin, streptomycin and sulfadiazine, with an eight hour interval for doses of penicillin and streptomycin for penicillin-resistant infections with, I believe, quite satisfactory results.

Dr. Frank L. Meleney, New York (closing): I appreciate very much the interest shown in the presentation, and thank the discussors for bringing up these points. Certainly the toxicity of bacitracin is of great importance and concern. I want to say a few words to indicate why I think this is not a factor of the bacitracin itself, but one of the byproducts of manufacture. In the first place, the material we made in our laboratotry with a synthetic medium showed no evidence of toxicity whatsoever.

The manufacturers began the preparation of bacitracin with the same method which we had used in the laboratory and one of them sent us a small quantity of material which likewise showed essentially no toxicity. However, the yield per cc. in this medium was not satisfactory from a commercial standpoint and the manufacturers began using a soy-bean medium. In this medium bacitracin was produced in five to ten times as high a titre per cc. All commercial lots so far have been made in this medium but, along with the bacitracin, toxic factors came through in the final product. However, the material made by the Ben Venue Laboratories by means of surface culture in bottles produced only transient albuminuria and temporary rises in retained nitrogen. We were becoming quite complacent about the importance of toxicity inasmuch as we were able to obtain a clinical response without appreciable evidence of kidney damage. Most of the cases reported in this paper were treated with bacitracin from this source. However, recently we have been using bacitracin made by the Commercial Solvents Corporation by the deep-tank method and, while we have been told that in all other respects the manner of manufacturing is essentially the same, this material is certainly giving more frequent and more prolonged toxic symptoms. Furthermore, different lots vary considerably in their toxicity. This is true of lots having the same potency titre. We know that the toxicity is greatly modified by the salt content. In our animal tests bacitracin dissolved in physiologic saline is very much less toxic than bacitracin dissolved in distilled water.

Bacitracin has not yet been obtained in a pure state but chemical analyses indicate that it is made up of a number of amino acids, some of which are natural while others are unnatural. The toxicity may likely be in the unnatural amino acids which

may be either removable or neutralizable. When bacitracin is put in the ultracentrifuge, certain heavy products are carried down which are toxic, while the bacitracin remains evenly distributed. Furthermore, a dializing membrane will hold back certain toxic products which are obviously not a part of the antibiotic itself. The toxicity problem will be very intensively studied in the course of the next two or three months.

It is surprising to me to hear Champ Lyons say that almost all of the infection problems can be met by combined therapy of the sulfonamides with either penicillin or streptomycin. Certainly many infection problems come to me which have failed to respond to all of these agents. In fact, many of the cases reported in this paper are in this category. Dr. Lehman's report on the work of Dr. Sandusky with gas gangrene is of particular interest and clearly indicates that bacitracin is able to prevent the development of gas gangrene in experimental animals. The late deaths of some of the survivors may be indicative of toxicity of this particular lot of bacitracin, or it may be due to some factor associated with the culture material used in the injection. The control animals did not live long enough to show these late effects. Until this toxic problem is solved it is essential that the systemic treatment of bacitracin should be administered only in those units which are properly set up for its appraisal and in those cases which have not responded to the other available methods for the treatment of infections.

PARALYSIS OF DEGLUTITION – SURGICAL CORRECTION

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THIS PRESENTATION HAS TO do with reconstructive work necessary to restore the power of swallowing in a patient who has sustained extensive cranial nerve injuries. In 1864, Hughlings Jackson [1] called attention to the homolateral paralytic association of larynx, soft palate, tongue and muscles of the neck, particularly the sternomastoid and trapezius. In 1891, Avellis [2] wrote on palate laryngeal hemiplegia, a syndrome which sometimes bears his name. Since then additional articles by Schmidt,[3] Tapia,[4] Broeckaert,[5] have stressed certain features resulting from involvement of the last cranial nerves.

Particularly Vernet [6] and Collet [7] in 1915 have written on the syndrome of the jugular foramen characterized by involvement of the last three or four cranial nerves. In 1917 Villaret [8] used his term, "the syndrome of the retroparotid space," and included lesions of the sympathetic together with the last four cranial nerves. From World War I similar injuries have been reported.

CASE HISTORY

The patient, a white male 43 years of age, presented himself with the complaint of an inability to swallow dating from the time of a gunshot wound three years before. The wound of entrance of a 38 calibre bullet was alongside of the left ala of the nose and from there the bullet had passed directly back to a position just beneath the scalp, 1 cm. to the left of the external occipital protuberance (Fig. 1). In its course the mandible on the left had been fractured. Tremendous hemorrhage was presumably due to division of the internal jugular vein, and he required several transfusions. A long period of infection about the jaw ensued and union was considerably delayed; some months were required before healing was complete. The bullet had injured and caused a paralysis of several nerves (Fig. 2). The anterior two-thirds of the tongue on the left was anesthetic from injury of the lingual branch of the trigeminal. Farther posteriorly, near the jugular foramen, it had encountered and paralyzed the ninth, tenth, eleventh and twelfth cranial nerves. As a result of the paralysis of the twelfth nerve, the left half of the tongue, in addition to being anesthetic, was atrophic. By reason of paralysis of the tenth nerve, the palatal movement on the left was absent and the left vocal cord was paralyzed so that his voice was hoarse, and the upper, middle, and inferior pharyngeal constrictors were paralyzed. With paralysis of the eleventh nerve, the supply to the left sternomastoid and trapezius was affected. The damage to the ninth nerve was responsible for anesthesia of the soft palate, nasopharynx and pharynx on the left. The stylopharyngeus muscle, which is the only muscle supplied by that nerve, was paralyzed.

Since the time of the injury the patient had been unable to swallow. He had learned to adjust himself and had become fairly well adapted to this, maintaining a

* Read before the American Surgical Association, May 29, 1948, Quebec, Canada.

fair state of nutrition with a liquid diet and regular use of a stomach tube. His most serious complaint was of strangling from excessive salivation. Since he was unable to swallow the saliva, it passed frequently into his larynx. This caused terrific explosions of coughing and vomiting, with regurgitation of the material into the nasopharynx and through his nose. Even with continued use of such drugs as atropine to lessen the amount of secretion, travel in public conveyances was almost prohibited because of the frequency and severity of these attacks. The patient was on the point of suicide.

It was apparent at once that numerous factors contributed to his disability. In the act of swallowing, the tongue rises and presses upward and backward; the soft palate closes off the nasopharynx, the larynx rises and its opening is covered by the epiglottis as the material passes into the upper portion of the esophagus. During and after World War I, occasional reports

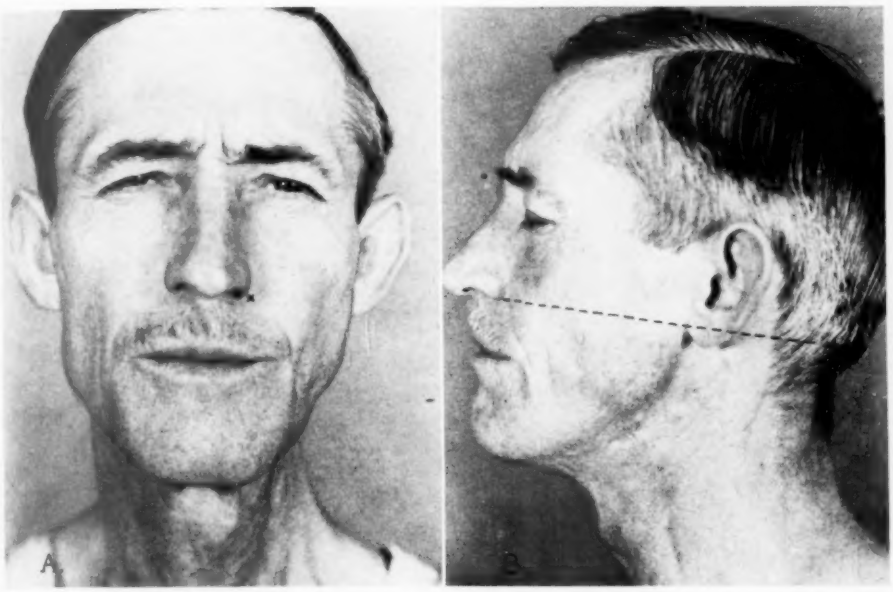

FIG. 1.—Showing course of bullet.

describing extracranial paralysis of the last four cranial nerves from bullet wounds appeared in the literature. We have been unable to find evidence of any surgical treatment which corrected such an inability to swallow.

Beginning with Majendi's work in 1813,[9] various theories of deglutition have been advocated. Majendi believed that ingested materials were forced from the mouth into the stomach by means of peristaltic-like muscular contractions of each area through which the bolus passed and that in effect the muscles of the mouth, pharynx and esophagus were active agents in propelling the food onward. He considered there were three stages: (a) a voluntary stage during which the mylohyoid and longitudinal lingual muscles contracted and enabled the tongue to propel the bolus past the fruces; (b) an involuntary, almost convulsive contraction of the pharyngeal constrictors

during laryngeal elevation which forced the material into the upper end of the esophagus and finally, (c) a slower, involuntary stage during which the bolus was driven along into the stomach by the esophageal circular fibers. In 1880 Kronecker and Falk [10] suggested that fluids and semifluids were projected by contraction of the muscles of the mouth (the mylohyoids) before the contraction of the pharyngeal and esophageal musculature occurred, and that this occurred later after the bulk of the bolus had passed and served to sweep along the remaining particles. Kronecker reported that

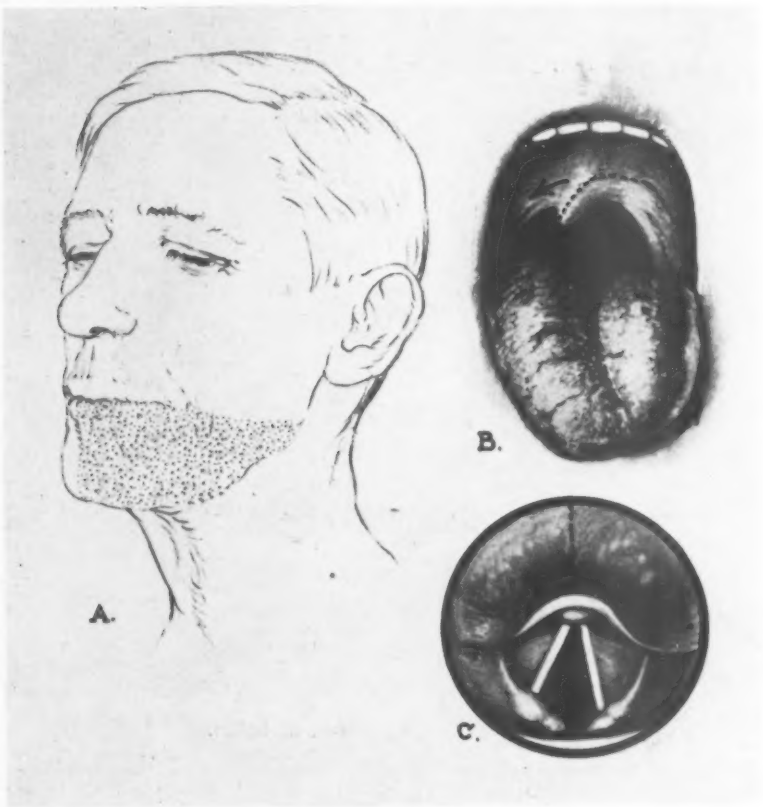

FIG. 2.—A. Dotted area of altered sensation from injury to inferior dental nerve and cervical branches. B. Atrophy of left half of tongue (twelfth nerve injury); deviation of uvula (tenth nerve); outline of anesthesia (ninth nerve). C. Adducted position of vocal cord (tenth nerve).

at the beginning of deglutition there was a rapid rise of manometric pressure, to 20 cm. of water, in the posterior mouth, pharynx and upper esophagus. By means of balloons in the pharynx and esophagus, they recorded the passage of the peristaltic wave some time after the descent of the ingested liquids.

Cannon,[11] in 1898 and 1900, showed that the act of swallowing varied

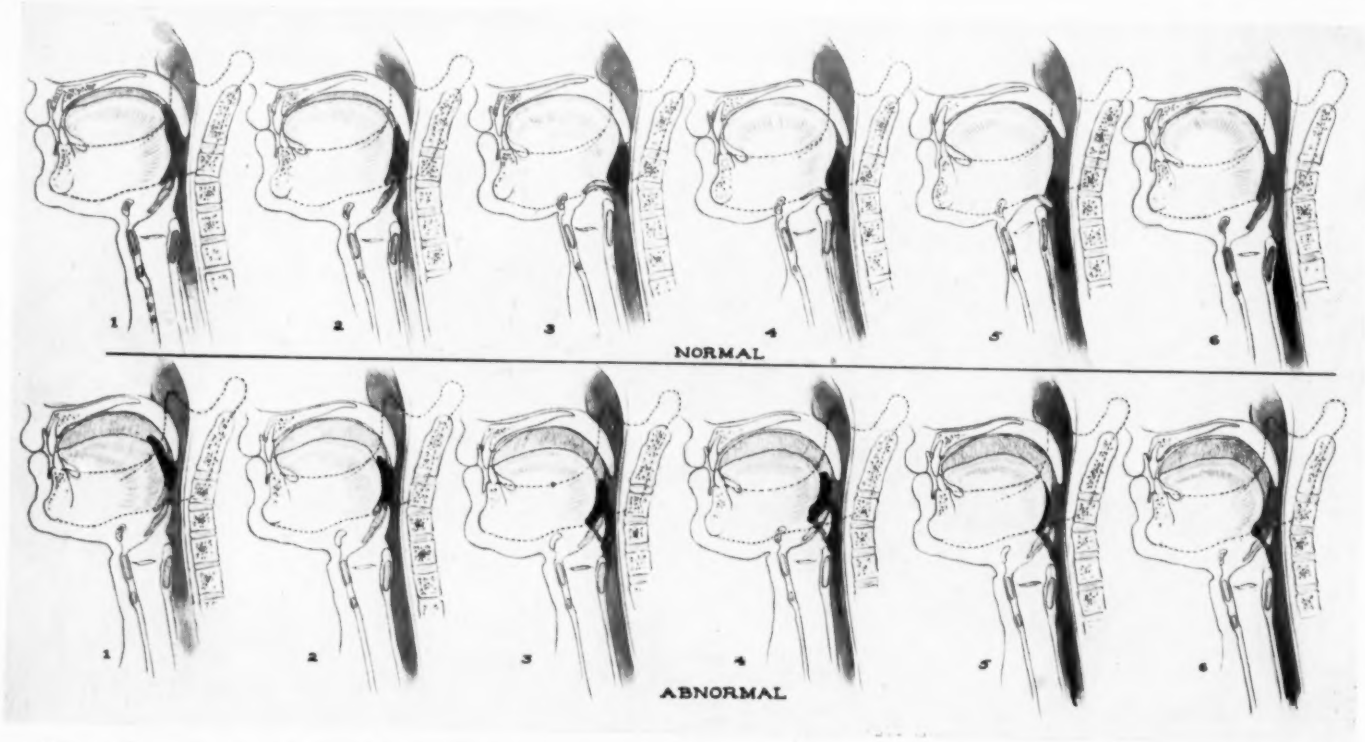

FIG. 3. NORMAL.—1 and 2. Bolus pressed against the soft palate occluding nasopharynx. 3 and 4. Tongue pressing up and back; larynx ascends; epiglottis occludes laryngeal opening as bolus passes; 4 and 5. Bolus passing into esophagus. 6. Larynx descended, epiglottis upright, bolus in esophagus. ABNORMAL—1 and 2. One half of tongue atrophied; nasopharynx not closed off by palate. 3 and 4. Oral cavity and nasopharynx not closed by tongue; larynx has ascended only partially; epiglottis remains upright. Bolus has passed into valeculae and pyriform sinus. 5 and 6. Bolus gradually trickles into esophagus.

with different vertebrates and with different consistencies of the ingested material. By means of roentgen-ray studies, he came to the conclusion in agreement with Kronecker and Meltzer, that in the human fluids were shot directly down to the cardia, mainly by the action of the mylohyoids and not by peristalsis, but that the swallowing of solids and semisolids was a slower peristaltic-like process. Deglutition in fowls was relatively slow and peristaltic and there was no mylohyoid squirting action. In the absence of such action a greater reliance on gravity was noted. For example, in dogs when the mylohyoids were denervated, fluids were no longer rapidly squirted into the esophagus, but it was necessary for the animal to raise its head and swallow, after the manner of a bird. In the horse and in man, it has also

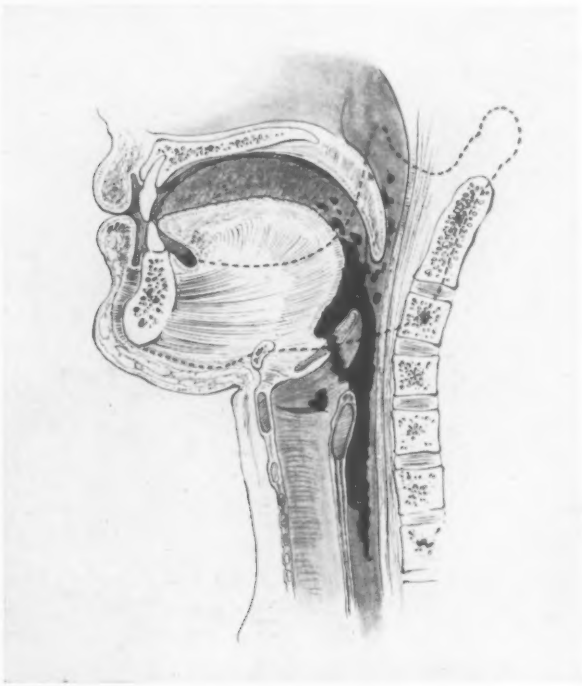

FIG. 4.—Barium scattered by coughing.

been noted that only fluids were squirted ahead by the mylohyoids before the peristaltic action occurs. Cannon described human swallowing of a solid bolus thus: When the food is sufficiently masticated, it is gathered in a depression on the dorsum of the tongue. The tip and lateral aspects of the tongue press against the hard palate and teeth, to prevent escape of food particles forward and laterally to the mouth and cheeks. Respiration is reflexly suspended. The tongue is pressed upward and backward by contraction of the mylohyoid and hyoglossus respectively (Fig. 3 Normal). The tongue, thus acting as a piston, drives the bolus first against the downward

sloping soft palate, next against the posterior pharyngeal wall, then on between this pharyngeal wall and the posterior surface of the upright epiglottis, the tip of which lies in contact with the base of the tongue. During this phase the action of the palato-pharyngeus muscles has thrown the pharynx into a narrow cleft and against this opening the soft palate is pulled by contraction of the levator palati, thus blocking entrance of the bolus into the nasal chambers. Thus far the esophageal opening has remained closed mainly by pressure of the larynx against it. With the rise of the hyoid and larynx, the esophagus opens. The epiglottis is pressed back until it shuts the laryngeal aperture. Then presumably the tip of the epiglottis

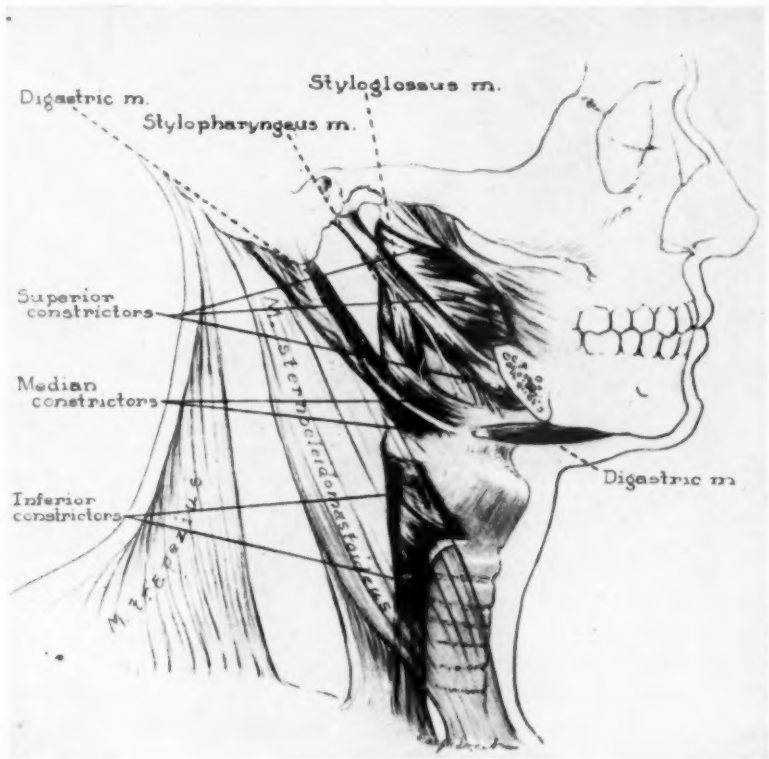

FIG. 5.—Final attachment of the posterior belly of the digastric in the human.

slips downward along the posterior pharyngeal wall, "pushing the bolus probably with a final quick impulse into the gullet." Whether or not the action of the epiglottis is a factor in pushing the bolus is a point that was disputed as far back as 1892 by Stuart.[12] Mosher,[13] in 1927, published studies from which he concluded that the epiglottis acts as a cover for the larynx during swallowing.

Fluoroscopic studies of our patient by Dr. Earl Miller demonstrated that the paralyzed pharyngeal constrictors bulged outward during the swallowing

effort and that barium accumulated and remained in the valleculae of each side of the base of the epiglottis. It was also apparent that the epiglottis remained upright and did not pass into a horizontal position to occlude the laryngeal opening. The barium trickled down from the valleculae on each side into the pyriform sinuses and occasionally small flecks passed into the larynx. Explosive efforts at coughing followed and observation after this showed flecks of the material scattered throughout the pharynx and in the

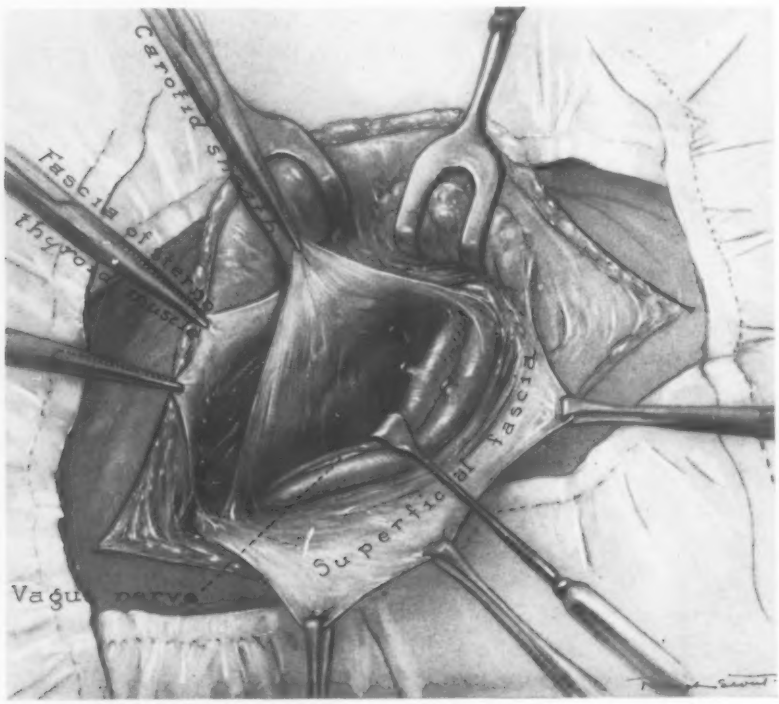

FIG. 6.—Fascial support of the lateral wall of the pharynx.

avrious pockets and in the nasopharynx (Fig. 4). The entire act of swallowing is so rapid that more detailed analysis was impossible. We found it necessary to secure more data on the normal act of swallowing before a satisfactory analysis could be made of the difficulties of our particular patient.

We were able to obtain the use of a fluoroscope synchronized with moving picture apparatus so that with this cine fluoroscope radiograms of deglutition could be taken at the rate of 60 to the second. Such studies were obtained of a normal individual and then upon our patient. It was possible then to study the motions of swallowing at intervals of one-sixtieth of a second and to compare the abnormal function with the normal (Fig. 3 Abnormal). It became evident that at least one important factor was that which prevented the epiglottis from assuming a horizontal position and closing the larynx during the act of swallowing. Although the larynx would rise during the

act of swallowing, its upward excursion was less than normal. The stylopharyngeus muscle, which is the only one supplied by the ninth nerve, passes down from the styloid process and inserts in the region of the larynx between the superior and middle pharyngeal constrictors. Its action in drawing the larynx upward had been lost through its paralysis. Other contributing factors were the bulging of the paralyzed pharyngeal constrictors on that

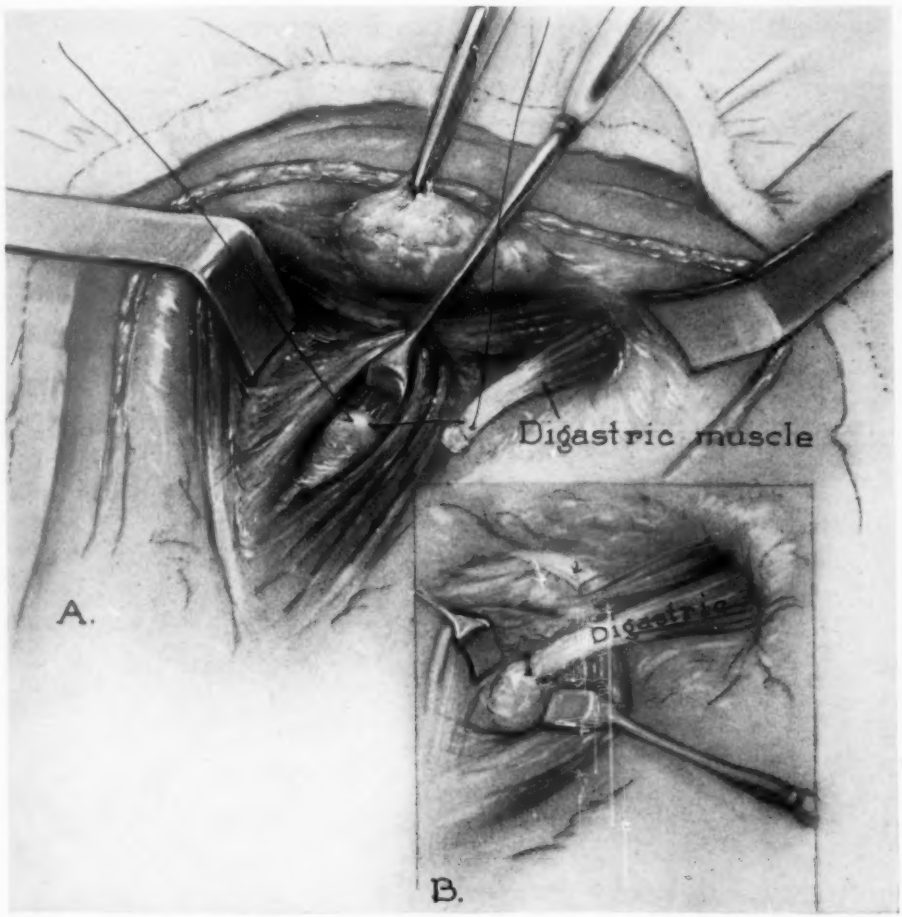

FIG. 7.—Digastric divided at the sling. Posterior belly sutured to laryngeal cartilage.

side and atrophy of the tongue. The pressure of the tongue on the epiglottis, which carries it down to a horizontal position, was impaired.

It seemed desirable, then, to reproduce the neurologic lesion in experimental animals and endeavor to find a solution for the difficulty. The anatomic arrangement in the dog was not suitable, but the macaque was found to be an appropriate animal. A similar lesion was produced by paralysis of the ninth, tenth, eleventh and twelfth nerves. Following this, the animal retained food in its mouth for 12 hours and was unable to

swallow. To prevent the lateral bulging of the pharynx, a fascial sling was devised which was attached to the prevertebral fascia posteriorly, then brought around the lateral pharyngeal wall and attached to the midline of the laryngeal and neighboring cartilages. In order to aid the upward movement of the larynx during swallowing, the posterior belly of the diagastric, which is innervated by the seventh nerve, was attached to the larynx to substitute for the paralyzed stylopharyngeus (Fig. 5). This was done in the animal and was followed by restoration of the ability to swallow. The

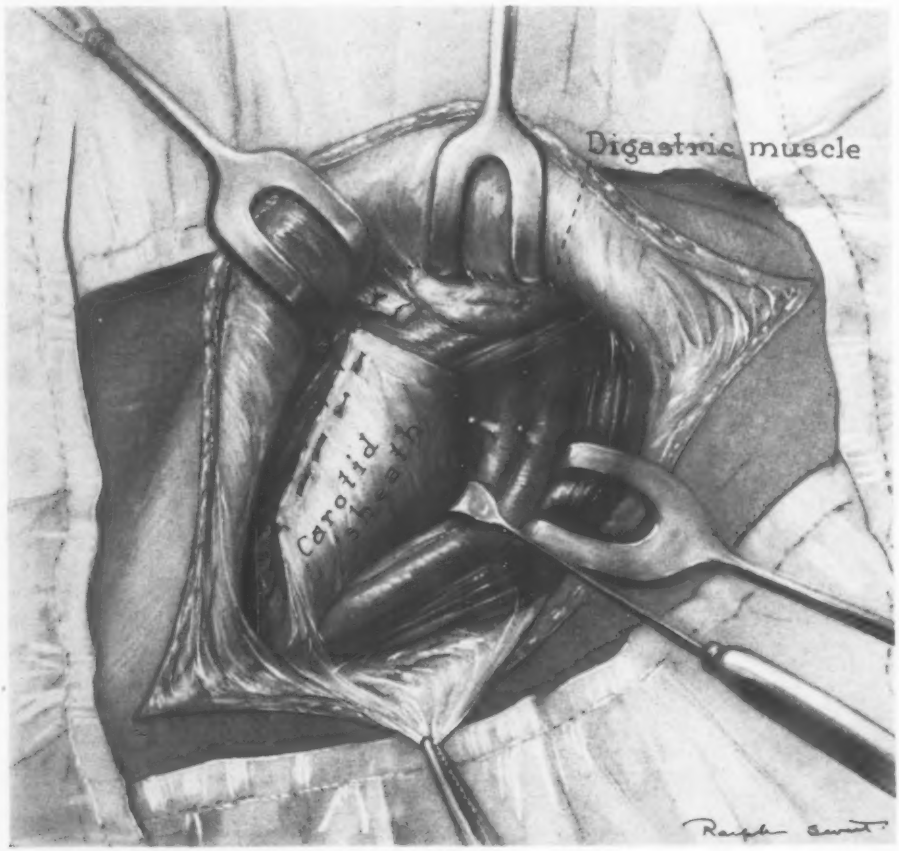

FIG. 8.—Carotid sheath reflected and sutured to midline to support the pharyngeal wall.

procedure was then planned for the human patient. (The seventh nerve was unimpaired.)

It was found that the use of a free fascial sling to wrap around the pharynx was not required, for by splitting the fascia of the neurovascular bundle from in front (Fig. 6) and dissecting away the mesial portion of it to its firm attachment to the prevertebral fascia, a free leaf was obtained which was then brought forward around the pharynx and fastened to the

midline of the larynx and cricoid. This gave firm support to that side of the pharynx. The posterior belly of the digastric was then cut loose from its junction with the anterior belly and firmly attached to the thyroid cartilage (Fig. 7) so that its contraction would cause ascent of the larynx. During the postoperative period the patient was taught to so grimace with the lower face that the digastric contracted at the instant of swallowing. By this maneuver, the larynx was elevated and the patient was trained to swallow. It has now been over two years since the operation and there has been no occasion to have recourse to the stomach tube. Swallowing is sufficiently satisfactory that the patient has been able to work in construction camps and partake of the more or less rough food which is available.

Advice, suggestions and help on the anatomic details and studies have been given freely by Professor Saunders of the Department of Anatomy. Research by the roentgen-ray studies has been carried out by Dr. Earl Miller.

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DISCUSSION.—DR. MAX PEET, Ann Arbor: I was much intrigued with this paper when Dr. Naffziger kindly allowed me to read it in advance, because I could see applications for this procedure in cases other than the very rare gunshot wounds. Occasionally we have tumors in the posterior fossa which produce almost identical symptoms because of paralysis of the vagus and, in some cases, of the hypoglossal in addition.

The difficulty in swallowing that these people experience is often their chief complaint. Many of these patients come to us so late that, although the tumor can be removed successfully, there is no chance for regeneration and, as you see the patient months and even years afterward, he begs for something to be done to aid him in swallowing. True, most of them do not have as much difficulty as this patient of Dr. Naffziger's, but they do have regurgitation of food into the nasopharynx, sometimes it even shoots out of the nose, or down into the larynx, and they have severe fits of coughing. This new operative procedure developed by Dr. Naffziger may be of great benefit to some of these patients.

However, it would not be of value in patients having great difficulty in swallowing and from whom very large acoustic tumors have been removed, because in such cases the 7th nerve has also been destroyed. This would preclude the use of the digastric muscle to elevate the larynx. This use of the digastric muscle in Naffziger's operation is a very clever method of elevating the larynx. Some other method will have to be found in individuals who have paralysis of the 7th as well as the 10th nerve.

I am particularly pleased to have this clear elucidation of the act of swallowing, a complicated procedure which was not understood before this splendid demonstration. The application of this special x-ray camera, taking pictures at one-sixtieth of a second, clearly demonstrates the actual process of swallowing. I am not sure of how much importance paralysis of the stylopharyngeus muscle is. Certainly in individuals with glossopharyngeal neuralgia we do not hesitate to divide the entire 9th nerve intracranially, which would include its motor branch to the stylopharyngeus muscle. These individuals do not have any difficulty in swallowing. I have divided both 9th nerves for bilateral glossopharyngeal neuralgia and no impairment in swallowing was evident. Perhaps the stylopharyngeus in the normal individual does act as the chief elevator of the larynx. However, in individuals with this muscle paralyzed, but without any other intracranial pathology, other muscles probably take over that function. In the case described by Dr. Naffziger the paralysis was so extensive that no regular muscle function could be substituted.

I do not know what other muscle could be used in place of the digastric to elevate the larynx, but certainly the fascial sling Dr. Naffziger devised to hold in the bulging pharyngeal muscles and prevent the pocketing which held so much food would be applicable. I am very much pleased that Dr. Naffziger had this opportunity to make such an important contribution.

LATE COMPLICATIONS FOLLOWING CRANIOPLASTY WITH ALLOPLASTIC PLATES*

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A COLLECTION OF STATISTICS on complications following cranioplasty with alloplastic plates was undertaken for presentation at the round-table discussion on cranial injuries held at the Clinical Congress of the American College of Surgeons in September 1947, under the chairmanship of Dr. A. Earl Walker. These have been augmented and further clarified during the intervening months. It is a pleasure to express my thanks and appreciation to the neurosurgeons of the Army, Navy, and Veterans Administration hospitals who have been so helpful in the collection of these data. In answer to a questionnaire, case reports were obtained on 151 late complications following the insertion of plates of tantalum, vitallium, and acrylic resin, which came into standard use in our military hospitals during the War.

An excellent article on the history and development of cranioplasty was published by Woolf and Walker[1] in 1945. They have reviewed past experience with the various technics for grafting bone and cartilage and experiments in the use of a great variety of strange materials such as horn, ivory, hard rubber, mica, plaster of Paris, etc. Early successful results are reported with silver, gold and celluloid. Silver through oxidation becomes mildly irritant; both it and gold are expensive and too soft for use in large plates. Silver has the added disadvantage of ultimately discoloring the overlying scalp. With the exception of celluloid, used with success by Ney[2] and Coleman,[3] plating with these substances had dropped out of use between the wars.

Tantalum came into use in 1941 after Burke[4] reported its use for buried surgical appliances and sutures and after the demonstration of its suitability for cranial repairs by Pudenz,[5] Hook[6] and Fulcher[7]. The first use of vitallium for repair of cranial defects was described by Geib[8], also in 1941. The use of methyl methacrylate resin (lucite or plexiglass) was developed experimentally by Kleinschmidt[9] and adapted to human cranioplasty in this country by Gurdjian et al[10] and by Kahn[11] in 1943. At the time of Woolf and Walker's review sufficient time had not elapsed to permit any survey of late complications from the use of these alloplastic plates which have proved to be so convenient for repairing such huge cranial defects as can be made by an airplane propellor, shell fragment, or kick of a horse. These concave gaps in the skull are unsightly, a source of risk from further trauma, and may give rise to much local discomfort and apprehension. Yet many questions in connection with their repair remain unanswered. What is the best materials to use? When is the best time for its insertion? What

* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

are the risks of displacement, late infection, cerebrospinal fluid leaks, pneumatocele, and epilepsy? These questions could not be answered in 1945 when Woolf and Walker's report was published. It is of interest also to note that plating with alloplastic material was never approved by the National Research Council. It has therefore been a stimulating challenge to attempt to obtain an answer to the late results of the great number of cranioplasties performed in the war two to six years after these plates were inserted.

SUMMARY OF REPORTED FAILURES

In July, 1946, Bradford and Livingston[12] reported eight patients seen at the Naval Hospital in Oakland who required early removal of tantalum plates because cranioplasty had been performed at too early a date in an infected field. These repairs had failed to heal and had drained persistently from the start. That late breakdown of the scalp was occurring following cranioplasty with plates of biologically inert metals and acrylic resin in a small proportion of cases first became apparent from a review by Lane and Webster[13] of the combined experiences at 22 Veterans Administration hospitals where 52 plates had been removed prior to April, 1947. In the series of 196 patients operated upon on Dr. C. W. Elkins' service at the Newton D. Baker General Hospital and followed by Dr. Thomas Holbrook (personal communication) up to their discharge from the Army, 6.1 per cent are known to have required removal of plates for secondary infection, and a total of 11.7 per cent had complications which required some form of surgical intervention. Experience at the Special Military Hospital for Head Injuries in Oxford has shown that 8.5 per cent of cranial defects repaired by tantalum plates have developed complications necessitating their removal in a two-year period of observation. These statistics are based on a review of 128 patients in whom 130 tantalum plates were inserted. Lewin, Graham, and Northcroft[14] were able to follow all but four of these men over a minimal period of two years, and have been kind enough to send me a copy of their manuscript prior to its publication. Although it has been impossible for the Office of the Surgeon General of the Army or the Bureau of Medicine and Surgery of the Navy to furnish statistics on the total number of cranioplasties performed in our military hospitals, I believe it is fair to assume that less than 10 per cent have been unsatisfactory. From the 151 reports of late complications summarized in Table I, together with the evidence submitted in the Oxford report, we are justified in drawing certain definite conclusions regarding the use of plates in the repair of cranial defects:

1. Complications from plates made of tantalum, vitallium, and lucite occur in practically the same proportion of cases. In Elkin and Holbrook's series these amounted to 10.6 per cent in 66 cranioplasties performed with lucite and 12.3 per cent in 130 after plating with tantalum.

2. Thin, scarred and inadequately vascularized scalp is likely to break down over a plate (Fig. 1).

3. Poorly fitted plates, or those that have not been securely fixed and have slipped, may erode the scalp (Fig. 2). The use of triangular metal points for fastening the plate have been a frequent cause of this complication. Vitallium or tantalum screws are superior, but even these can become loose if the plate has not been properly fitted and exerts constant traction on the screw.

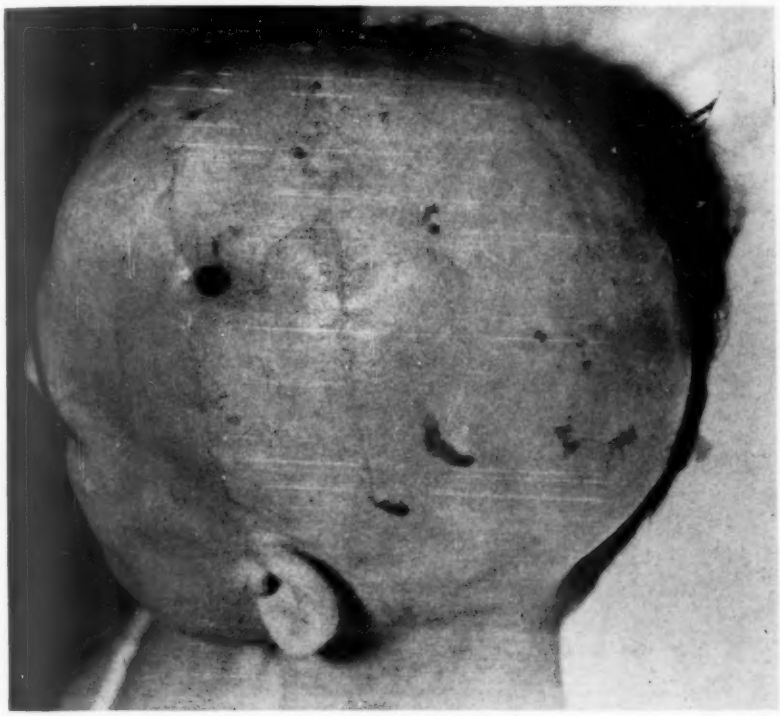

FIG. 1.—Thin, poorly vascularized scalp, which broke down at junction of two poorly constructed flaps sutured under tension to cover defect over vitallium plate.

The plate beneath was drilled in hopes that granulations would grow through from underlying dura. This failed and plate was finally removed; prompt healing followed.

Resultant scar was so firm that no secondary plate was needed to cover 4 cm. defect in skull.

(Patient of Dr. J. C. White, U. S. Naval Hospital, St. Albans.)

4. Plates should be perforated at frequent intervals to permit escape of underlying fluid and its absorption by the lymphatics of the scalp; also in order to secure better fixation by fibrous union between the dura and galea. A number of surgeons reporting have commented on the frequency of complications in unperforated plates. In a few instances, solid plates giving rise to trouble have been successfully replaced immediately after multiple

drill holes were made. Ulmer reports from the McGuire V. A. Hospital (personal communication) that plates, if properly perforated, may even heal in place after separation of the overlying scalp. In four complications where the scalp broke down because of scar formation and infection, the plates "healed over with the assistance of buds of tissue growing up through the perforations while the infection was controlled by antibiotics."

5. Perforations in the dura-arachnoid may result in leakage of spinal fluid around the plate and require secondary repair (Fig. 3). The im-

FIG. 2.—Large, poorly fitted plate, whose prominent lower edge compressed and eroded scalp. Removal of plate and partial closure were followed by uneventful but slow healing.
(Courtesy of Dr. Loyal Davis, V. A. Hospital, Hines, Mich.)

portance of water-tight dural closure to prevent accumulation of cerbrospinal fluid under the plate has been emphasized in the Oxford report. Lewin et al[14] have even suggested that the presence of a metallic plate may lead to excessive secretion.

6. Plates inserted over the frontal sinus or mastoid may lead to trouble if air leaks into the tissue or there is secondary acute infection. Harris and Woodhall[15] have reported two instances of extradural pneumatocele from residual defects of the frontal sinus. I have information on one case

of late infection around a supraorbital plate following acute frontal sinusitis. In a previous review of complications with 52 plates which necessitated removal, Lane and Webster,[13] neurosurgical consultants in the Veterans Hospital at Dearborn, Michigan, have found that in approximately half frontal plates have been at fault (Fig. 4). Furthermore, in 18 of these the defect involved the frontal sinus. In those cases reported in Table I in which the position of the plate is known, frontal plates gave rise to one-third of

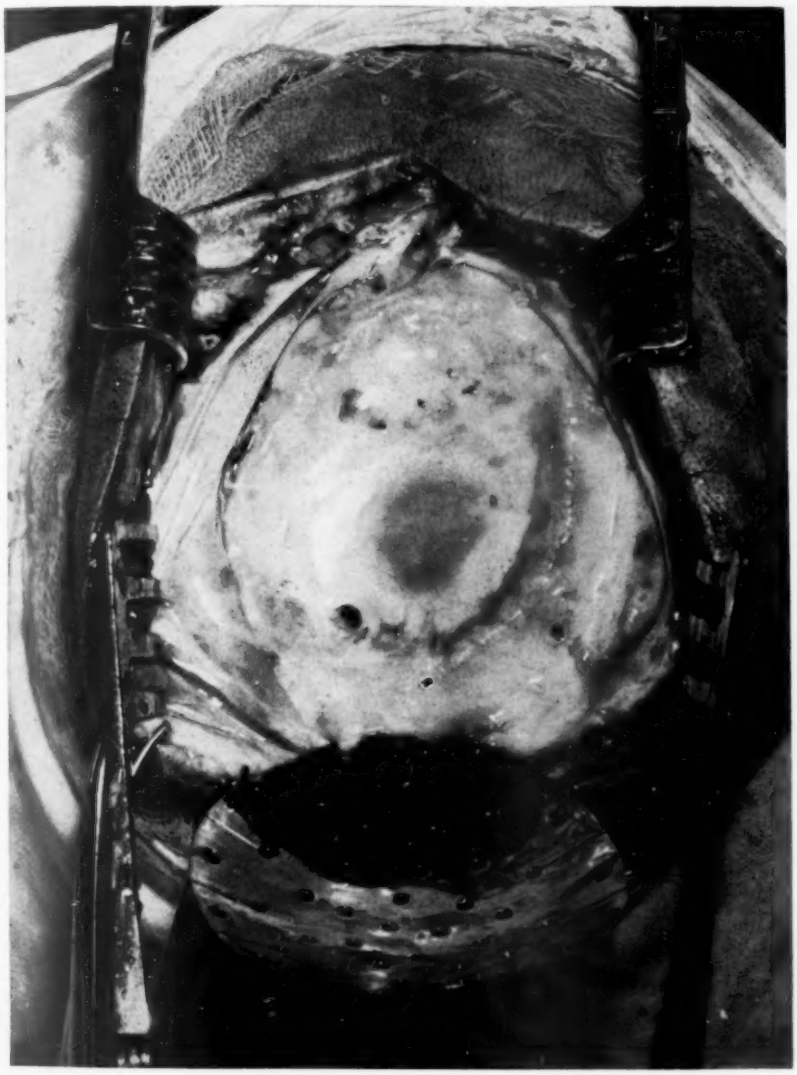

FIG. 3.—Small defect from imperfect dural closure, which permitted persistent reaccumulation of cerebrospinal fluid under vitallium plate. After fascial patch plate was replaced. Healing and late result have been satisfactory for over two years.

(Courtesy of Dr. T. I. Hoen, U. S. Naval Hospital, St. Albans.)

the complications. The inadvisability of repairing defects which involve the frontal sinus and brow ridge is confirmed in this larger series and also in the Oxford report.

7. Trauma to scalp over the plate and also secondary plastic operations have resulted in loss of overlying tissue and necessitated removal (Fig. 4). In one instance the plate was actually stove in as a result of direct trauma in an automobile accident.

8. There have been a few reports that metallic plates have caused discomfort on exposure to extreme heat or cold. Figure 5 illustrates such a complication with shifting of the loose plate as an added factor. Substitution of an acrylic plate securely anchored by screw fixation has given a satisfactory result.

FIG. 4.—Erosion of thin tissue over brow ridge with infection and exposure of tantalum plate, following a secondary plastic procedure. Removal of plate and evacuation of epidural abscess were followed by uneventful healing. (Courtesy of Dr. Loyal Davis, V. A. Hospital, Hines, Mich.)

9. The onset of convulsive seizures secondary to cranioplasty with alloplastic plates is not a complication to be feared. Epilepsy unquestionably due to the presence of a plate has been reported in only a single case observed by Dr. Hannibal Hamlin from the U. S. Naval Hospital at Chelsea (personal communication). In this patient a plate had previously been inserted to cover a 5 cm. defect three months after drainage of a cerebral abcess. Latent infection developed and the plate was removed, but the surgeon made the mistake of inserting tantalum foil to cover the dural defect. This sailor developed severe convulsions. On reexploration the tantalum foil was removed together with a dense fibrous scar tightly adherent to underlying brain. The dural defect was reconstructed and a new tantalum plate fitted. He has remained seizure free on dilantin for two years.

In a certain proportion of these cases there is no explanation for the appearance of swelling and tenderness over the plate months after its insertion other than reactivation of latent primary infection. In many of these cases it has been obvious that the plate was inserted too early following healing of an infected wound. In some roentgen rays revealed the presence of indriven bony fragments and metallic foreign bodies which had not been

removed. Dr. T. I. Hoen (unpublished cases seen at U. S. Naval Hospital, St. Albans), like Bradford and Livingston, had to remove five of these plates in patients in whom cranioplasties had been performed at too early a date in advanced hospitals in the Pacific. In addition, Woodhall, Pilcher, German, Meirowsky, and others (personal communications) have observed instances where cranioplasty was performed at too early a date. It is evident that Gardner's[16] suggestion of primary plating at the time of operation for active

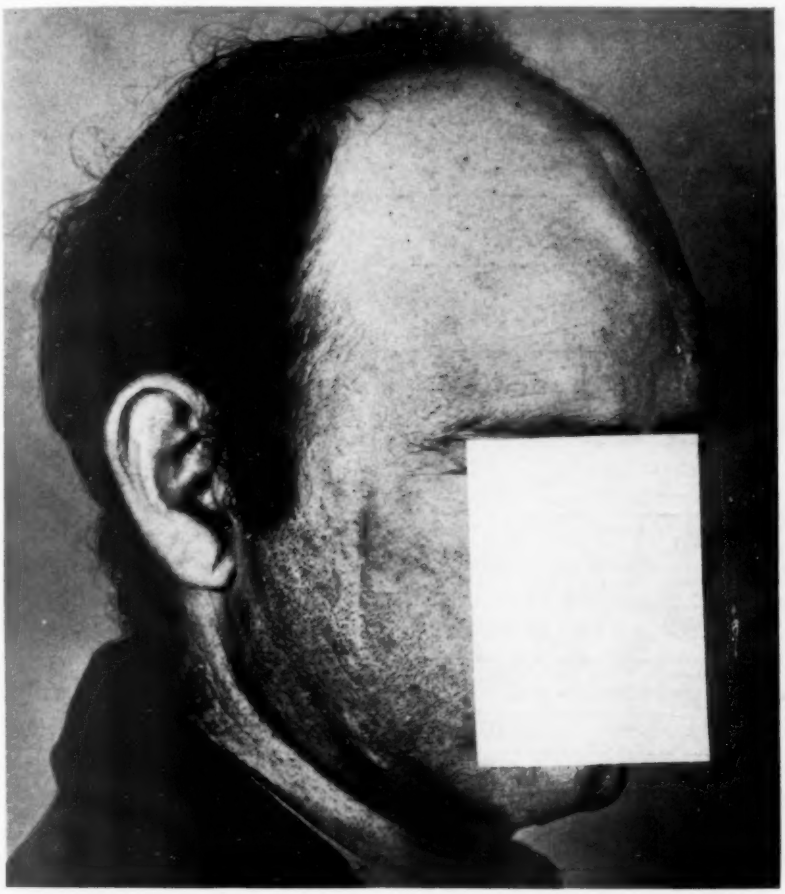

FIG. 5.—Tantalum plate covering defect in frontal bone, which had slipped and caused discomfort on exposure to heat and cold. This was replaced by acrylic resin plate fixed in place by screws, with satisfactory result. (Courtesy of Neurosurgical Service, Cushing V. A. Hospital, Framingham, Mass.)

osteomyelitis and cerebral abscess is a definite departure from sound surgical principles.

Fortunately infection that has developed around these plates has usually been mild and osteomyelitis of the exposed bone in the edge of the defect has never been a serious problem. In patients where the repairs have broken

TABLE I.

CASES REPORTED FROM	Total No. of Cases	Infected	Non-Infected	Plate Preserved	Plate Removed	Later Re-plating	Loss of Secondary Plate	Frontal Plates Causing Complications	Pneumatocele	Brain Abscess	Death	Epilepsy due to Complication	COMMENT
U.S.N.H., Chelsea, Mass. (Dr. H. Hamlin)	2	1	1	..	2	..	..	1	..	..	..	1	Seizures due to cerebral cicatrix around tantalum foil used for dural substitute.
U.S.N.H., Oak Knoll (Dr. W. J. German)	6	6	..	1	5	..	..	..	..	..	..	..	
U.S.N.H., St. Albans (Drs. J. C. White and T. I. Hoen)	10	8	2	1	9	1	..	..	..	1	1	..	Pt. with abscess moribund on admission.
Newton D. Baker Gen. Hosp, W.Va. (Dr. Thomas Holbrook)	23	20	3	11	12	..	..	..	..	..	..	..	Material: 66 lucite, 130 tantalum.
Aspinwall V.A.H., Pa. (Dr. S. N. Rowe)	2	2	..	..	2	..	..	..	..	..	..	..	
Bronx V.A.H., N.Y. (Dr. E. G. Krueger)	11	10	1	..	11	1	..	4	1	1	..	..	Cortical abscess formed under tantalum foil used to cover defect in dura.
Crile V.A.H., Cleveland, O. (Dr. P. P. Partington)	3	1	2	1	2	1	..	1	..	..	..	..	Cerebrospinal fluid leak through dural defect. Another plate stove in by trauma.
Cushing V.A.H., Framingham, Mass. (Neurosurgical Service)	5	5	..	..	5	..	..	3	..	..	..	..	One tantalum plate replaced by lucite because patient claimed disagreeable sensation heat and cold.
Dearborn V.A.H., Mich. (Dr. G. S. Bates)	3	3	..	..	3	..	..	2	..	..	..	..	One infection due to acute frontal sinusitis.
Hines V.A.H., Mich. (Dr. L. Davis)	14	14	..	..	14	1	1	..	..	..	..	..	
Jefferson Barracks V.A.H., Mo. (Dr. R. D. Woolsey)	4	3	1	..	4	..	..	1	..	..	..	..	One plate exposed by trauma; one broke down because of retained cotton pledget; one poor fit.
Kennedy V.A.H., Memphis, Tenn. (Dr. A. M. Meirowsky)	5	5	..	..	5	1	..	1	..	..	..	..	Two epidural granulomas suggested toxic reaction.
Lawson V.A.H., Chamblee, Ga. (Dr. G. Perret)	5	5	..	1	4	2	..	2	..	..	..	..	
Los Angeles V.A.H., Calif. (Dr. W. A. Jones)	4	4	..	1	3	1	..	1	..	1	..	..	Abscess caused by retained loose fragment of bone.
McGuire V.A.H., Richmond, Va. (Dr. J.L. Ulmer)	12	10	2	6	6	..	..	1	..	..	..	..	Two non-perforated plates replaced at once after drilling.
Mendota V.A.H., Madison, Wis. (Dr. L. E. Trent)	1	1	..	..	1	..	..	..	..	..	..	..	
Miami Beach V.A.H., Fla. (Dr. W. T. Haverfield)	4	1	3	2	2	2	..	1	..	..	..	..	
Minneapolis V.A.H., Minn. (Dr. H. F. Buchstein)	1	1	..	..	1	..	..	1	..	..	..	..	
Salt Lake City V.A.H., Utah (Dr. R. Harrow)	1	1	..	..	1	1	..	..	..	..	..	..	
Wadsworth V. A. H., Kan. (Dr. L. T. Gathman)	1	1	..	..	1	..	..	..	..	..	..	..	
Washington V. A. H., D.C. (Dr. H. V. Rizzoli)	2	..	2	1	1	..	..	1	..	..	..	..	Sharp edge of fixation point eroded scalp, cerebrospinal fluid leak around tantalum point.
White River Junction V.A.H., Vt. (Dr. H.L. Heyl)	3	3	..	..	3	..	..	..	..	..	..	..	One plate slipped so that it indented dura.
Winter V.A.H., Topeka, Kan. (Dr. L. L. Bernstein)	2	2	..	..	1	..	..	1	..	1	1	..	Death from infection following primary plating at another hospital. Patient entered moribund with abscess under temporal plate.
Wood V.A.H., Wisconsin (Dr. D. Cleveland)	5	5	..	..	5	1	1	..	..	..	..	..	
Dr. W. McK. Craig, U.S.N. Hosps.	1	1	..	..	1	1	1	..	..	..	..	..	
Dr. E. F. Fincher, U.S.A. Hosps.	8	8	..	4	4	1	..	..	..	..	..	..	
Dr. H. C. Naffziger, San Francisco.	1	1	..	..	1	..	..	..	..	..	..	..	
Dr. C. Pilcher, Nashville	4	4	..	..	4	..	..	..	..	..	..	..	
Dr. B. Selverstone, U.S.A. Hosps.	3	3	..	3	..	..	..	..	..	..	..	..	
Dr. B. Woodhall, U.S.A. Hosps.	5	3	2	3	2	..	..	2	2	..	..	..	Successful pedicle graft to cover defect.
	151	132	19	35	115	14	3	23*	3	4	2	1	

* These 23 occurred in 69 cases where the location of the plate was specified.

down, simple removal of the plate together with underlying granulations and devitalized bone or loose fragments, followed by primary closure (with or without brief drainage), chemotherapy and local and systemic penicillin, has usually resulted in prompt healing. If the cranial defect has been a small one, fibrosis has usually made secondary plating unnecessary, but it can be carried out successfully after a delay of six months to a year. Only three out of 14 secondary plates have been lost.

Two deaths have resulted from the insertion of plates which may be ascribed to definite errors in surgical judgment. One occurred in a late neglected spreading suppuration around a plate inserted overseas. This sailor arrived moribund at St. Albans with an underlying intracerebral abscess. The other, reported from a Veteran's Hospital, had had a plate inserted immediately following late secondary debridement of osteomyelitis and a granulating wound with loose bony fragments. He was discharged soon thereafter, but re-entered another hospital in a moribund condition from underlying abscess of the brain. Two other abscesses beneath plates have been reported from the Veterans' Hospitals. These have responded well to early and adequate drainage.

LESSONS TO BE DERIVED FROM EXPERIENCE OF WORLD WAR II

There are certain obvious lessons that we should learn from these experiences. Late complications, as shown above, have occurred most frequently after plating the frontal bone, especially in reconstructions of the orbital ridge. To construct and secure in place a perfectly fitting plate in this area is a difficult technical feat. In addition, this region is particularly susceptible to trauma and infection from the frontal sinus and nasal cavity. Complications from these sources are likely to occur as long as the patient lives. Breakdown of the thin skin in the upper eyelid with infection of the plate occurred in one nervous individual who picked at a prominence over the edge of his plate while studying. Reconstruction by bony grafts is not as likely to make trouble on these scores, and I think we should consider a change in policy in this type of cranioplasty. From what I have learned from this review I shall henceforth use grafts of autogenous bone for repair of the orbital ridge, but continue to use metallic plates for covering extensive defects in the frontal bone above the level of the sinus.

When swelling and tenderness have developed after an apparently successful plating, treatment by aspiration and penicillin have occasionally been followed by subsidence of infection when the organism has been penicillin sensitive and there has been no other predisposing factor such as slipping of the plate, inadequate circulation of the scalp, or communication with the frontal sinus. In the presence of a granulating sinus with exposure of the underlying plate, it is usually best to sacrifice the plate without delay, although in 26 cases of this series chemotherapy and plastic procedures have been followed by ultimate healing. I would recommend immediate removal

of any plate which is grossly infected or has underlying loose bone or metallic fragments to avoid the risk of infection penetrating the dura and serious risk to the patient or unnecessarily prolonged hospitalization. Time in hospital can be saved by taking out the plate and replacing it at a later date if so desired. In the case of small plates underlying fibrosis will often result in sufficient rigidity to make this unnecessary.

With the possible exception of repair of the brow ridge and defects in direct contact with the frontal sinus, I see no reason why we should return to the use of grafts of autogenous bone. Two deaths have followed the injudicious insertion of metallic plates in the stage of active infection, but no other fatal complications have been reported. Grafts of living bone are more difficult to insert and the cosmetic result after covering extensive defects is never as satisfactory. Reactivation of latent infection may also take place after their use. If even minor sepsis develops, the grafted bone will be lost, which has not been universally true of metallic plates. In addition these grafts occasionally soften and lose their shape after an apparently successful take (Ney[2]; Grant and Norcross[17]).

If alloplastic plates are to be used, what material is best? Experience at Newton D. Baker General Hospital (C. W. Elkins and T. Holbrook, personal communication) and my personal observations at the U. S. Naval Hospitals at Chelsea and St. Albans and the Veterans Administration Hospitals in New England have shown that tantalum, vitallium, and acrylic resin give rise to complications of the same order and frequency. Tantalum is by far the easiest to process and fit at the time of operation. I have preferred it for this reason to vitallium and lucite, which once cast can only be subjected to minor alterations. In epileptic subjects, however, the roentgen-ray translucent lucite plates should be used to permit subsequent study by air injection if the seizures continue.

It appears advisable not to attempt a primary repair after craniocerebral trauma, but to wait for at least two months if the wound heals by first intention. If there has been initial infection, plating should be deferred for at least six months, and longer in cases of infection with penicillin-resistant bacteria. Even greater conservatism should be used in cases where the first plate has had to be removed. In those extremely rare instances where infection has developed a second time, as well as in primary repair of defects involving the frontal sinus, the substitution of bone for metal should be considered. Thin grafts of cancellous bone taken from the iliac crest, recommended by Mowlem[18] and Carmody[19], are especially well adapted for the repair of troublesome defects in the cranial vault. In all secondary cranioplasties it is extremely important that the overlying scalp be revised to eliminate areas of thin scar and deficient circulation. Leaks in the dura-arachnoid or communications with the frontal sinus must be searched for and closed; the plate, if reinserted, must be a perfect fit and fastened so

securely that it can never slip. All such operations should be followed by intensive use of both antibiotics and the sulfa compounds.

Insertion of metallic plates should be postponed for a long period in subjects who are likely to develop epilepsy. This complication, of course, most frequently occurs after deep wounds with dural penetration, indriven bony spicules or metallic fragments, and added sepsis. In these it is obvious that cranioplasty should be deferred because of the risk of reactivating infection. It would seem wise under these circumstances to wait at least a year and then to use roentgen ray transparent plates of acrylic resin, if there has been any history of seizures or evidence of an epileptogenic focus in the electroencephalogram. If this precaution is neglected, late epilepsy developing in the presence of a cerebral cicatrix and resistant to anticonvulsant drugs may necessitate removal of an otherwise satisfactory metallic plate in order to permit investigation of the cicatrix by pneumoencephalography.

CONCLUSIONS

The task of evaluating late complications following cranioplasty has been an interesting one. It is evident that a considerable number of alloplastic plates have led to complications (151 cases collected to date). The great majority of these have not been serious. Plastic closure of the defect in the scalp supplemented by chemotherapy in 35 cases and removal of the plate in the others has resulted in uncomplicated healing in 114. In four cases where plates were injudiciously inserted in septic fields infection spread through the meninges with cerebral abscess formation and death in 2 of the patients. Epilepsy has not resulted from the proper use of plates.

The majority of complications due to latent foci of infection have probably made themselves manifest by now, but a certain small number of patients with plates are liable to trouble as long as they live. This may follow trauma and laceration of the overlying scalp or infection from the underlying frontal sinus or mastoid. Under this circumstances grafts of living bone would presumably be tolerated better. Complications of this sort have been rare.

The most common complication after cranioplasty is infection or necrosis of the overlying scalp. This may occur after grafts of living bone as well as after insertion of plates of biologically inert metal or acrylic resin. In addition, grafts of bone may soften months or years after an apparently successful take. The causes of failure after plating and precautions necessary to prevent it have been discussed. The facts disclosed appear to justify the conclusion that a safe, simple, and satisfactory repair of a large cranial defect can be accomplished better and with no greater risk by an alloplastic plate than by grafts of cartilage or bone. When the cranial defect involves the frontal sinus, however, a return to the use of grafts of living bone is recommended.

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DR. WILDER PENFIELD, Montreal: I think Dr. White has done well to call attention to the necessity of observing surgical principles in the handling of plates and foreign bodies. It is necessary to be particularly careful of the ordinary surgical principles when dealing with a foreign body. One must be quite sure that the danger of infection is passed, that the circulation of the scalp and underlying dura is adequate. In our experience we have felt it better to close the dura, not to use any foreign body to fill in the dural defect, but to make sure that there is as nearly as possible complete closure of the dura so that there will be no connection between the spinal fluid and the plate. It is true that plates do not produce post-traumatic epilepsy so far as one can tell, and yet we have seen a good many patients in whom post-traumatic seizures began very shortly after insertion of a plate which was put in, often for reasons that are difficult to determine. When a man is getting along quite well with a little hole in his skull, he or his wife or someone wants it closed. I think we should be quite strong against such closure unless there is good purpose in it. I feel

that the use of tantalum plates is a real step forward provided proper principles are observed.

Another use for which we have found tantalum satisfactory is the following: We cut small disks not bigger than a button to go into the trephine or burr holes. That prevents eventual absorption and avoids excavation which otherwise appears in the scalp. Such indentations in the bald scalp of a friend, I have found very embarrassing. When bone disks or chips are used the telltale excavation always appears. Tantalum disks avoid that. The smaller the foreign body the less likely it is to give rise to trouble. I have seen many of these plates inserted that were much larger than need be. If the size is minimum the subsequent complications are reduced to a minimum.

Dr. Howard Naffziger, San Francisco: This presentation of Dr. White's includes a good many of the points stressed by our President in his address. Tantalum plates have a place, but I think they do not have as many places as are found for them. A good deal of the work in Veterans Hospitals in the neurosurgical line has had to do with removal of these plates as well as removal of the tantalum material placed about peripheral nerve suture lines.

In connection with the last point Dr. Penfield mentioned I would like to suggest that for small defects the use of mesh screen of tantalum or stainless steel is useful. This need be not much larger than a postage stamp, perhaps twice the size. There is a minimum of foreign material, the soft tissues grow through, and the cosmetic effect is good. As good, I believe, as with solid material. It can be shaped with scissors at the table and be put in in a moment. We have used this for several years to cover small defects that would otherwise be visible.

Dr. Gilbert Horrax, Boston (closing): I want to thank Dr. Penfield and Dr. Naffziger for discussing this paper, and I agree with them both in the things they have brought out. I was brought up in a school which did not believe in cranioplasty of any kind. I saw Dr. Cushing put in only one metal plate in 20 years and I think, as a matter of fact, that that had to come out. Any defects which were apparently conspicuous we occasionally filled in with bone. Bone does not make as neat and as nice a covering as tantalum, however, and I think in cases such as those mentioned by Dr. Penfield and Dr. Naffziger there is a definite place for this type of material, because it does make a very perfect contour of the skull such as it is impossible to get with any type of bony material.

THE CLINICAL ASPECTS OF CHRONIC THYROIDITIS*

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CHRONIC THYROIDITIS is not a rare disease, although any one surgeon may see few cases. Our excuse for reviewing the clinical aspects stems from our very low percentage of correct preoperative diagnosis, and the fact that we at times failed to recognize the pathology even when exposed at operation. We believe that chronic thyroiditis is *not* to be classed as a pathological curiosity, that it is an important matter from the clinical standpoint, and that it is most important for the patient that the situation is fully recognized at operation. Surgical sins, in this connection, are usually those of commission rather than omission, that is, too much is done. We were anxious that our Interne and Resident group be made well aware of this condition, and that our Attending Staff should aim at a higher percentage of correct preoperative diagnosis. We therefore reviewed 34 case records of thyroiditis from the Surgical Service at Roosevelt Hospital, and would like to present a few brief observations in regard to them.

We are not concerned with acute thyroiditis, (with or without suppuration), nor with specific infections such as syphilis, tuberculosis, actinomycosis, etc., but only with the obscure so-called "non-specific" chronic thyroiditis. Many excellent reviews of this general group are to be found, but nearly all deal largely with histopathology and etiology [16, 17, 20]. Most cases fall readily into three subgroups: (1) The struma lymphomatosa of Hashimoto[12] (occurring about once in every hundred routine thyroid operations). (2) The struma fibrosa, described by Riedel[19] more than 50 years ago (somewhat less common than the first group), and (3) the rarer giant cell type of De Quervain[18]. Much argument has been advanced to the effect that all these represent different phases of the same process, but the facts do not support this view and it seems to us that the division is clinically sound and useful. We have omitted the eight cases of acute thyroiditis (two with suppuration) from our group for this study, and also two cases in which the lymphoid changes in the gland were marked but still focal, leaving only 24 cases of undoubted chronic non-specific thyroiditis for detailed appraisal. We would like to offer a brief review of the features of each of the three groups.

For a complete picture of Hashimoto's disease one should read Joll's superb Hunterian lecture on the subject[14]. The condition is characterized by a diffuse lymphocytic involvement of the thyroid gland, with germinal centers, and widespread destruction of the thyroid cells. (One sees *focal* lym-

* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

phoid accumulations in many cases of Graves disease, and in other thyroid conditions, but careful study easily differentiates these glands from the Hashimoto group.) Hashimoto's disease is extremely rare in males, and occurs chiefly in women at or near the menopause. It seems to be a degenerative process, rather than inflammatory. Adhesion to surrounding structures does not occur. The thyroid is usually diffusely enlarged, and the patient has some discomfort and a sense of "fullness." Pressure symptoms are mild. There is apt to be early myxoedema, although it is likely that, in the very early stages, there may be a transient hyperthyroidism. The thyroid, in Hashimoto's disease, is firm but not hard, is grayish pink in color, and finely lobulated, but does not contain distinct nodules. Its cut surface is yellowish. Among our 11 patients with the Hashimoto type of thyroiditis the usual story was that of slight discomfort, often intermittent, and usually more definite on one side than the other. In some the glands were quite large; in nearly all they were larger than normal; but in one case the size was within normal limits. We often felt sure, before operation, that one or both lobes were nodular, but the findings at operation revealed true nodularity in only one case. The lobes often resembled very large lymph nodes. The blood supply was usually less than normal. In one case, presenting a large diffuse struma lymphomatosa, lymphosarcoma followed partial resection after several months. Even in retrospect, the original sections were puzzling. This sequence is very rare, but has been reported by others[14].

After a positive diagnosis, roentgen-ray therapy may be given with good results. Our own practice has been a symmetrical conservative type of resection. Extensive resection is unnecessary and unwise. In any event thyroid feeding will probably be needed.

Riedel's disease, or struma fibrosa, occurs in both sexes, but predominantly in women. It seems to be inflammatory in origin and the process spreads over the gland like a slow fire. The uninvolved portion of the thyroid is apt to be normal, and fairly normal thyroid function is thus preserved. The involved portion is pale and stony hard, presenting dense masses of fibrous tissue, and it is usually very adherent to the surrounding structures. This feature causes the trouble and the story is one of constriction. Freeing of the trachea, by tedious and careful excision of the isthmus, is often indicated — no more need be done, but the condition is often confused with malignancy and unwise and harmful surgery may follow. In Riedel's original case a false impression of malignancy was gathered. He attempted total extirpation but soon abandoned the idea due to technical difficulties, and was amazed that the patient continued to live and prosper. One of the early patients in our own series did not fare so well, for the impression of malignancy led to a total extirpation, with permanent loss of recurrent nerve and parathyroid function. If the frozen section diagnosis is doubtful, one should wait for permanent sections before further surgical removal is undertaken.

The rarer type of thyroiditis, the giant-cell type of De Quervain[18], also appears to be of inflammatory origin. The patient is likely to have real pain. Involvement of the thyroid is limited to certain areas and there is some tendency to adherence to surrounding structures. The gland is *not* stony hard as in the Riedel type. The nature of the giant cells has been a matter of much dispute[7, 8]. The picture may closely simulate tuberculosis and has been

FIG. 1.

FIG. 2.

FIG. 1.—Two types of Riedel's disease, from Joll's book Diseases of The Thyroid Gland: On the left, adherent muscle, and thyroid tissue "choked" by dense whorls of hard white fibrosis. On the right, the gradual slow progression of the process, with normal thyroid remaining at the lower pole.

FIG. 2.—Gross specimen of lobes from our Case 1. The picture, both gross and microscopic, was typical of Hashimoto's disease. Several months later the remnants began to grow rapidly, having become lymphosarcoma.

called "pseudotuberculous thyroiditis." In the two cases of this sort in our series the pathology was confined to the right lower portion of the thyroid gland. It caused considerable discomfort with tracheal irritation. In one the frozen section diagnosis was neoplasm. Only a conservative resection was done and the permanent sections indicated the proper classification. She has remained well for more than 13 years. Recent reports indicate that roentgen-ray therapy, following a positive diagnosis may be the treatment of choice in this type[5].

CHRONIC NON-SPECIFIC THYROIDITIS

CASE HISTORIES

Case 1.—A. S.: A 30-year-old white female entered the hospital, with presenting symptoms of diffuse swelling of the anterior neck, difficulty in respiration, and some pain of one month's duration. Physical examination showed marked symmetrical enlargement of the thyroid gland without fixation to the surrounding

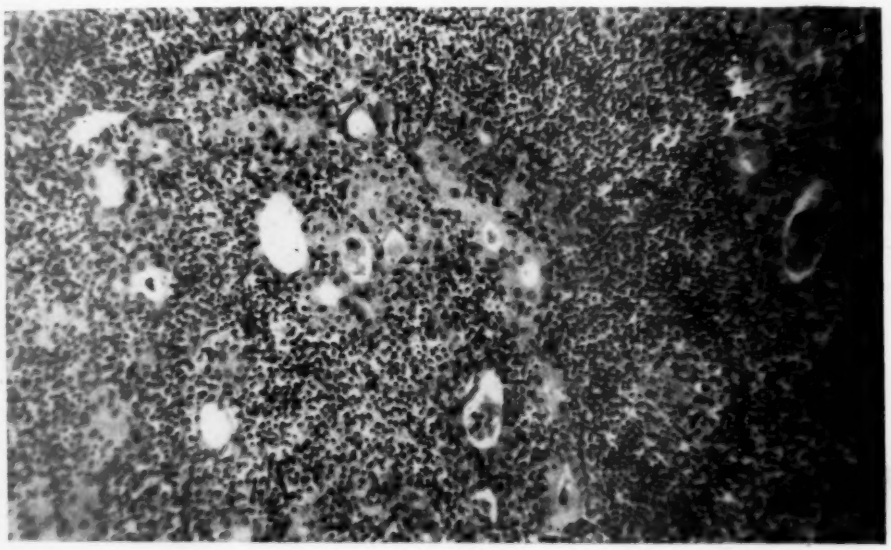


FIG. 3.—Section from Case 1, showing what we thought to be an extensive Hashimoto type thyroiditis. The thyroid remnants soon became lymphosarcoma.

structures. There was no evidence of toxicity. BMR was normal. Preoperative diagnosis was diffuse non-toxic goiter. Treatment was subtotal thyroidectomy leaving large remnants. The postoperative diagnosis was Hashimoto's struma. This diagnosis was made by three different competent pathologists. (Fig. 2, 3.) Within a few months this patient died in another hospital of generalized lymphosarcoma, known to involve the thyroid gland, the neck, the mediastinum and abdomen.

Case 2.—M. L.: A 50-year-old white female entered the hospital with the presenting symptoms of pain and fullness in the right anterior neck, of 18 months' duration. Physical examination revealed a firm, tender nodule in the right lobe of the thyroid gland. The patient had been suffering from low grade hypothyroidism and had a BMR of minus 9. The clinical diagnosis was thyroiditis. The operation was partial thyroidectomy, of a conservative type. The postoperative

diagnosis was Riedel's struma. The patient has been well since the operation and has no complaints.

Case 3.—J. D.: A 50-year-old white female entered the hospital with the presenting symptoms of enlargement of the right side of the thyroid, associated with pain of about 14 months' duration. Physical examination revealed a gland which was rather firm. The BMR was plus 9. The preoperative diagnosis was diffuse goiter, questionably toxic. The operation was subtotal thyroidectomy. Postoperative diagnosis was Riedel's struma. (This patient had had a mastectomy in Warsaw in 1939 for carcinoma of the breast.)

Case 4.—D.M.: A 53-year-old white female entered the hospital with the presenting complaint of a lump in the lower anterior neck of one year's duration. Physical examination revealed a firm, symmetrical, smooth thyroid gland about twice normal size. This patient had slight lidlag and the left eye was weak in convergence. The preoperative diagnosis was diffuse, mildly toxic goiter. Treatment was subtotal thyroidectomy. It is interesting to note that the thyroid gland extended most of the way around the trachea and the gland tissue removed weighed 108 Gm. In spite of this the patient had no symptoms of pressure. The postoperative diagnosis was Hashimoto's struma. (Fig. 4.)

Case 5.—N. S.: A 62-year-old white female entered the hospital with the chief complaint of a mass in her neck of about two months' duration. Physical examination revealed a firm, ovoid mass in the left side of the neck which was not tender. This patient had been suffering from chronic sinusitis for many years. The preoperative diagnosis was non-toxic nodular goiter. Treatment was excision of a firm nodular area in the lower pole of the left lobe of the thyroid gland. Postoperative diagnosis was Hashimoto's struma. The patient has been well since her operation with no complaints referable to the thyroid gland.

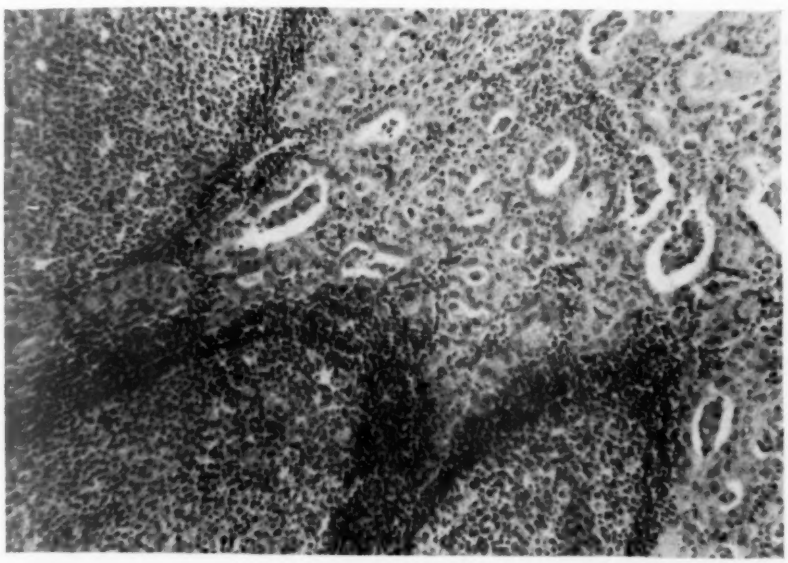
Case 6.—I. D.: A 51-year-old white female entered the hospital with the following complaints; swelling in the neck and pressure in the back of the throat of eight weeks' duration. Physical examination revealed a firm swelling in the right lobe of the tyroid. The BMR was minus 21. Preoperative diagnosis was non-toxic nodular goiter. The treatment was subtotal thyroidectomy, with the removal of only a small amount of each lobe. The postoperative diagnosis was Hashimoto's struma. Since the operation the patient has been taking thyroid extract, grains 1½ every day, and has continued to be somewhat unstable emotionally, as she was preoperatively. A BMR repeated six months after operation was minus 28.

Case 7.—M. S.: A 52-year-old white graduate nurse entered the hospital with the chief complaint of swelling in the anterior neck, particularly on the left, associated with difficulty in swallowing, of four days' duration, plus some hoarseness for the same period of time. Physical examination revealed an enlargement of the left lobe of the thyroid with some definite tenderness. The BMR was minus 11. The diagnosis at this time was acute thyroiditis and tonsillitis. The patient was treated with warm saline gargles and penicillin but this did not give complete relief of the thyroid symptoms. Because of the persistence of the swelling and the difficulty in swallowing, a left subtotal hemithyroidectomy, including the isthmus, was done. At operation it appeared that the trachea was shifted to the right and the left lobe was enlarged and yellowish-pink in color. The diagnosis of Hashimoto's struma was made at operation. It is interesting to note that this patient had been bothered for a good many months with chronic tonsillitis and that about six months prior to this current hospital admission she had had a similar bout of swelling in the region of the thyroid. After leaving the hospital the patient did very well. Her BMR was minus 14 twenty months after operation. She has no clinical signs of hypothyroidism in spite of the lowered basal

metabolism. She has worked steadily except for a few weeks following an operation for gallstones.

Case 8.—M. G.: A 35-year-old female entered the hospital with the presenting complaints of nervousness, slight pain and swelling in the anterior neck, particularly on the right, of about six months' duration. This patient also had mild difficulty in swallowing and slight difficulty in breathing during exertion. Physical examina-

FIG. 4.



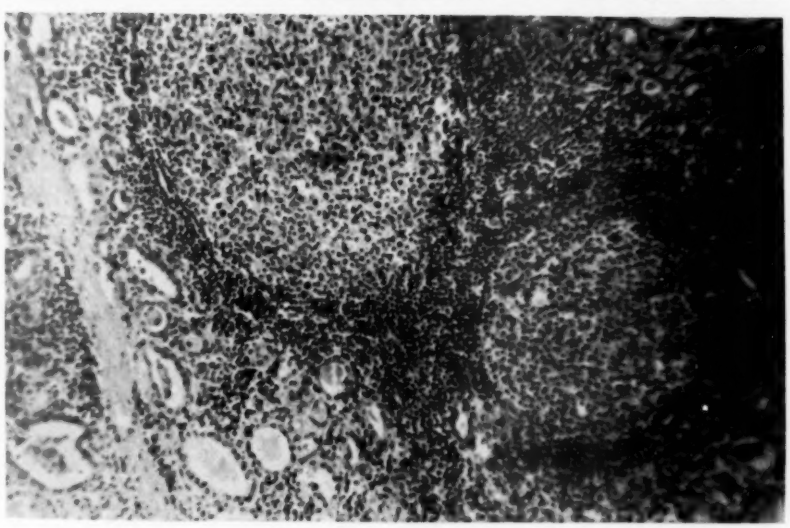


FIG. 5.

FIG. 4.—Case 4. Section showing large germinal centers, and infiltration of remaining areas of thyroid tissue in Hashimoto's struma.

FIG. 5.—Case 16. Typical section showing Hashimoto type thyroiditis. It is easy to see why these patients all tend toward myxoedema.

tion revealed moderate enlargement of the right lobe of the thyroid gland. This area was slightly tender and firm. The patient had slight tremor of the hands and the pulse was 100. The BMR was plus 9. The preoperative diagnosis was low grade toxic nodular goiter or possibly thyroiditis. During the operation the thyroid looked as if it were involved in a malignancy or a Riedel's struma. The gland was whitish-yellow in color and rather firm. The right lobe of the gland was very hard. A right partial thyroidectomy including the isthmus was done. A frozen section at operation showed Riedel's struma and so it was decided to leave the left lobe in situ. The left lobe was freed from the trachea. Postoperative diagnosis was Riedel's struma. Since operation the patient has felt fine but has had to take about 2 grains of thyroid extract every day. BMR since operation has varied from minus 7 to minus 20.

Case 9.—E. H.: A 56-year-old white female entered the hospital with the following complaints: lump in the right thyroid lobe, nervousness, weight loss and occasional tenderness in the right lobe of the thyroid for about 6 months. Physical examination revealed a diffusely enlarged right lobe of the thyroid with a hard nodule in the region of the isthmus. The entire gland was quite firm. BMR was plus 2. A preoperative diagnosis was nodular, non-toxic goiter, with other choices of malignancy and Riedel's struma. The treatment was conservative bilateral partial thyroidectomy. At operation the gland was pale, firm and rather avascular in appearance. It was yellowish-gray in cross section with islands of what appeared to be normal thyroid tissue. Postoperative diagnosis was Riedel's struma. The BMR 6 years after operation was minus 27. The patient feels somewhat tired but has no other definite symptoms of hypothyroidism. The patient has been advised to take thyroid extract but has refused to do this.

Case 10.—E. L.: A 21-year-old female entered the hospital with the following complaints: a lump in the neck of five months' duration, pain in the neck of two months' duration, laryngeal stridor, dysphagia, cough, hoarseness and chronic pharyngitis of seven weeks' duration. This patient had had osteomyelitis of the jaw one and one-half years ago. This patient had been treated in another hospital seven weeks prior to entry here. The treatment in the other hospital was directed towards her pharyngitis. BMR on admission here was minus 19. The preoperative diagnosis was Riedel's struma. Treatment was division of the isthmus of the thyroid with removal of the isthmus and a wedge of each lobe of the thyroid gland. The gland was adherent to the surrounding tissues and frozen to the trachea. This patient's preoperative tracheal constriction was so severe that a tracheotomy was considered at the time of operation.

Case 11.—K. S.: A 20-year-old white female entered the hospital with the following complaints: diffuse swelling of the anterior neck, and slight prominence of the eyes of several months' duration and menorrhagia of five years' duration. Physical examination revealed bilateral firm enlargement of the thyroid gland to three times normal size. The BMR was plus 13. The treatment was subtotal thyroidectomy. Preoperative diagnosis was diffuse toxic goiter of mild degree. Postoperative diagnosis was Riedel's struma with some areas of moderate hyperplasia of the gland.

Case 12.—H. W.: A 43-year-old white female entered the hospital complaining of intermittent hoarseness and choking associated with painful swelling in the left side of the neck anteriorly. There was also discomfort in swallowing. Physical examination revealed moderate enlargement and irregularity in shape and consistency of the thyroid gland. The left lobe was larger than the right and there were some dilated veins over the anterior neck. The BMR was minus 10. Preoperative diagnosis was non-toxic nodular goiter. Treatment was left subtotal thyroidectomy with removal of the isthmus. Postoperative diagnosis was Hashi-

moto's struma. Since operation the patient has had occasional discomfort in the neck, but no evidence of hypothyroidism and no thyroid extract has been required.

Case 13.—E. M.: A 47-year-old white female entered the hospital with the chief complaint of a lump in the thyroid region, some hoarseness necessitating the frequent clearing of the throat, irregular menses of four years' duration, weight loss and slight increase in nervousness. All of this was of two years' duration except the prolonged irregular menses. Physical examination revealed diffuse enlargement of the thyroid gland, most marked in the region of the isthmus. The BMR was minus 13 preoperatively. The preoperative diagnosis was non-toxic nodular goiter. Treatment was total thyroidectomy with tracheotomy. It is interesting to note that the operator believed he was dealing with an extensive thyroid carcinoma. In cross section the gland was grayish-white, and contained hard nodular areas. The right lobe was quite adherent to the trachea and surrounding muscle. The frozen section at the time of operation seemed to indicate a carcinoma of the thyroid. Upon leaving the hospital the patient had a complete left cord paralysis and a slightly paralyzed right cord. The final pathological diagnosis was Riedel's struma.

Case 14.—A. H.: A 49-year-old white female entered the hospital with the chief complaint of a pulsating mass in the right neck of six-years' duration. Physical examination revealed a diffuse enlargement of the thyroid gland most marked on the right. BMR was minus 14. Treatment was subtotal thyroidectomy. At operation a large nodule of the right lobe of the thyroid gland seemed to move with each pulsation of an underlying atypical carotid artery. The artery was not dilated. The postoperative diagnosis was Hashimoto's struma in an involuted nodular thyroid gland. After leaving the hospital the patient had no complaints and has not needed any thyroid extract. Her BMR was plus 1 seven months postoperatively.

Case 15.—A. T.: A 40-year-old white female entered the hospital complaining of a mass in the thyroid of 20 years' duration, with a slight increase in its size in the last few months. Physical examination revealed a rounded firm enlargement of the right lobe of the thyroid. The gland was freely movable. Preoperative diagnosis was thyroiditis, a first choice because of the firmness and tenderness of the thyroid gland, with neoplasm as second choice. Treatment was right partial thyroidectomy, and release of the left lobe of the thyroid from the trachea. Postoperative diagnosis was Hashimoto's struma. (Fig. 5.) After leaving the hospital the patient has had very low grade hypothyroidism. She is otherwise well.

Case 16.—S. T.: A 45-year-old-white female entered the hospital with the following complaints: lump in the anterior neck of one year's duration, fatigue and dyspnea of two years' duration, dysphagia of one year's duration. Physical examination revealed a rather diffusely enlarged thyroid gland most pronounced on the right behind and below the clavicle. BMR was minus 27. Preoperative diagnosis was adenoma of thyroid. Treatment was right subtotal thyroidectomy. Postoperative diagnosis was Hashimoto's struma.

Case 17.—A. T.: A 71-year-old white female entered the hospital with the following complaints: constant irritation of the throat with constant desire to clear it, cough, fullness in the anterior neck and variation in the size of the swelling of six months' duration. Physical examination revealed firm areas in the right lobe and isthmus which were not very mobile. Preoperative diagnosis was first, carcinoma of the thyroid, and second Riedel's struma. Treatment was right partial thyroidectomy with removal of a wedge of tissue from the left lobe and freeing of the left lobe from the trachea. The lower pole of the right lobe was adherent to the trachea in the region of the right recurrent laryngeal nerve. Postoperative diagnosis was chronic thyroiditis of the DeQuervain type. Since leaving

the hospital the patient has been well except for a long standing high blood pressure. She has been followed for 14 years since operation.

Case 18.—B. S.: A 50-year-old white female entered the hospital with the complaint of swelling and pain in the thyroid region. The patient had lost 20 pounds weight, was nervous and perspired a great deal. She had also had amenorrhea for the past six months and other associated menopausal symptoms. BMR preoperatively was plus 11. Preoperative diagnosis was mildly toxic nodular goiter, or carcinoma of the thyroid. Treatment was right partial thyroidectomy. At operation the right lobe was very hard and yellow but not adherent. Because of the large giant cells and the similarity to the picture of tuberculosis, the pathologist was prompted to do several sections and stained them for bacilli but none were found. (Fig. 6.) The postoperative diagnosis was chronic thyroiditis of the DeQuervain type.

Case 19.—C. W.: A 73-year-old white female entered the hospital with the chief complaint of a "lump" in the neck of two months' duration. Physical exami-

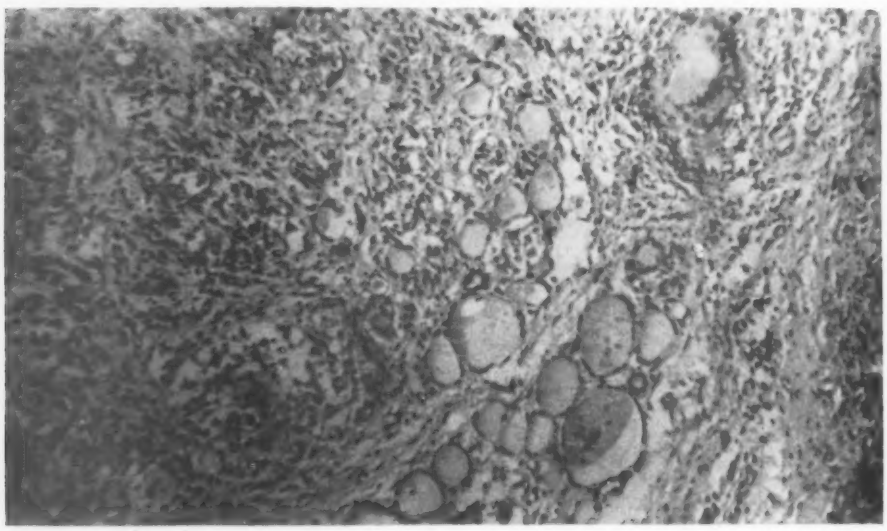


FIG. 6.—Section from Case 18, near the advancing edge of the process. Riedel's disease closely resembles this type, but it really belongs in the "giant-cell" or "Pseudotuberculous" thyroidits group.

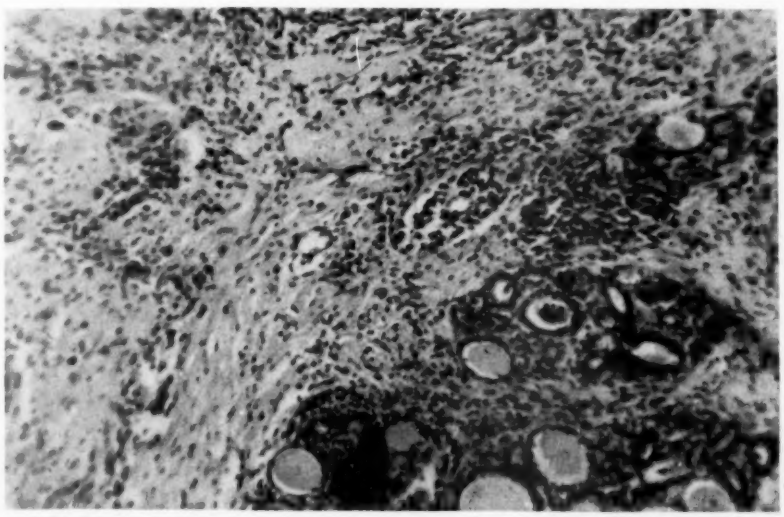
nation showed two firm areas in the thyroid gland. BMR was plus 7. The patient had had an upper respiratory infection and had it at the time of entry. Preoperative diagnosis was non-toxic nodular goiter. Treatment was subtotal thyroidectomy. At operation the gland was very hard, nodular and gray. Frozen section was done at this time because the gland looked as if it might be the seat of a primary neoplasm. This patient had had a history of intermittent cervical adenitis of many months' duration prior to this hospital entry. Postoperative diagnosis was Riedel's struma. BMR preoperatvely was plus 7. Two months' postoperatively it was minus 17 and the patient was taking one grain of thyroid extract every day, but had no obvious symptoms of hypothroidism.

Case 20.—C. F.: A 21-year-old white female entered the hospital with the chief complaint of a painful mass in the anterior neck of one year's duration. Physical examination revealed a firm swelling of the thyroid gland most marked on the right. The patient had allegedly lost 20 pounds. BMR was minus 18. Pre-

operative diagnosis was non-toxic nodular goiter. Operation was subtotal thyroidectomy in two stages. Both stages were very conservative. BMR after the second operation was minus 25. In the interval between the first and second operation the left lobe of the thyroid had increased considerably in size. Postoperative diagnosis was Hashimoto's struma. Since leaving the hospital the patient has been well and has taken a half grain of thyroid occasionally when she feels tired. There is no real picture of hypothyroidism.

Case 21.—R. D.: A 48-year-old female entered the hospital with the chief complaint of swelling in the neck of five months' duration following extraction

FIG. 7.



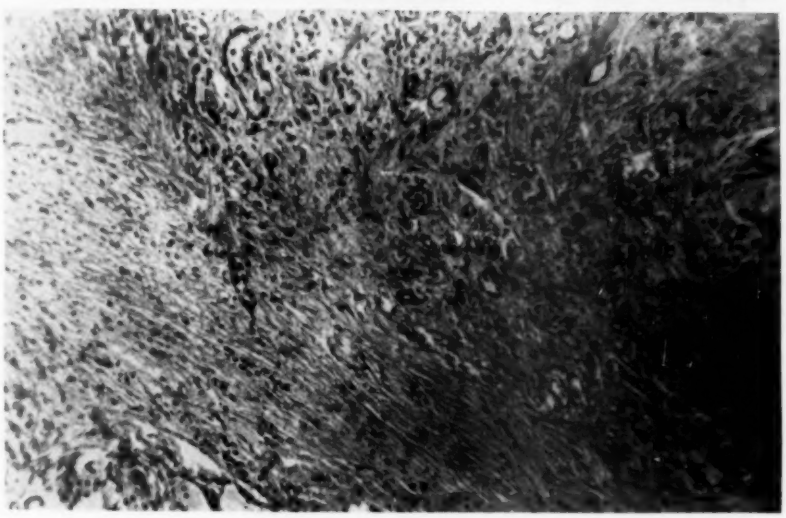


FIG. 8.

FIG. 7.—Section from Case 21. Reidel type chronic thyroiditis.
FIG. 8.—Section from Case 23. Reidel type showing advanced replacement of thyroid acini by dense fibrous strands.

of teeth. The patient allegedly lost 30 pounds. She was nervous, complained of pressure symptoms in the neck and had a temperature of 101 on entry into the hospital. Physical examination revealed a diffusely enlarged, irregular, hard thyroid gland. A preoperative BMR was minus 6. Preoperative diagnosis was non-toxic nodular goiter or a possible malignancy. Treatment was subtotal thyroidectomy. The specimen was gritty hard in appearance. (Fig. 7.) Postoperatively BMR was plus 5. Postoperative diagnosis was Riedel's struma.

Case 22.—C. M.: A 38-year-old white female entered the hospital with the chief complaint of a painful and marked swelling of the anterior neck of three weeks' duration. The patient was also nervous, had a tremor and had allegedly lost 40 pounds. Physical examination revealed a firm, tender, enlarged thyroid gland. BMR was plus 38 on one occasion and plus 29 on another. Preoperative diagnosis was diffuse toxic goiter or possibly thyroiditis. Treatment was a wedge shaped removal of a piece of each lobe plus bisection of the isthmus. Postoperative diagnosis was Riedel's struma.

Case 23.—M. N.: A 47-year-old white female entered the hospital with the chief complaint of an enlarged thyroid of 18 years' duration with a two months' story of a rather sudden increase in the size. Physical examination revealed an enlarged, rather irregular thyroid, particularly on the right. There was no apparent pain. BMR was minus 5. Preoperative diagnosis was non-toxic nodular goiter. The operation was biopsy of the right lobe and excision of the isthmus plus a wedge-shaped excision of each lobe in the region of the trachea. (Fig. 8.) At operation, the muscles were very adherent to the gland. The trachea was freed with difficulty. Postoperative diagnosis was Riedel's struma. Since operation the patient has been well and she has had no complaints, and no evidence of hypothyroidism.

Case 24.—L. D.: A 35-year-old white female entered the hospital complaining of fatigue and enlargement of the thyroid gland, particularly on the right. Physical examination revealed an enlarged, firm gland. Treatment was subtotal thyroidectomy. Preoperative diagnosis was diffuse, mildly toxic goiter. Postoperative diagnosis was Hashimoto's struma, with a few areas of slightly hyperplastic thyroid tissue.

SUMMARY OF THE CLINICAL ASPECTS OF 24 CASES OF CHRONIC NON-SPECIFIC THYROIDITIS

In 24 proven cases of chronic thyroiditis there were 11 cases of Hashimoto's struma, 1 of which became lymphosarcoma, 11 cases of Riedel's struma and 2 cases of pseudotuberculous thyroiditis of DeQuervain (giant cell type). The average age of the Hashimoto's cases was 43.8 years, of the Riedel's cases 44.2 years and the DeQuervain cases 61 years. All these cases were white women. 10 of the 11 cases of Hashimoto's struma (91%) showed enlargement of the gland, and all cases of the Riedel's and DeQuervain types showed enlargement of the gland. Pain or tenderness in the thyroid gland occurred in 7 of the 11 (64%) of the Riedel cases, 5 of the 11 (45%) of the Hashimoto cases and 1 of the 2 (50%) of the DeQuervain cases. Pressure symptoms such as hoarseness, dysphagia, dyspnea or choking occurred in 6 of 11 (55%) of the Hashimoto cases, in 5 of the 11 (45%) of the Riedel's cases and 1 of the 2 (50%) of the DeQuervain cases. The duration of symptoms in the Riedel group averaged 8 months,

in the Hashimoto group 5 months and in the DeQuervain group 6 months. One patient died, a mortality of 4.2%. This patient died of lymphosarcoma which involved the thyroid gland, mediastinum, etc. This patient's original diagnosis was Hashimoto's struma. The correct clinical diagnosis was made in 3 of 11 (28%) of both the Hashimoto's and Riedel's groups and in neither case of the DeQuervain type. The diagnosis of malignancy of the thyroid gland preoperatively or at operation before the pathological report was available occurred in 6 of the 11 (55%) cases of the Riedel's group, 1 of the 11 cases (9%) of the Hashimoto's group and in 2 of the 2 cases (100%) of the DeQuervain group.

SUMMARY AND CONCLUSIONS

Thirty-four case records of "thyroiditis" have been reviewed from the surgical service at Roosevelt Hospital. Deletion of the acute cases, and of 2 in which the pathology was rather limited, left 24 cases of undoubted "non-specific chronic thyroiditis" for detailed study. Eleven were of the Hashimoto type (struma lymphomatosa), 11 of the Riedel type (struma fibrosa), and 2 of the giant-cell type of DeQuervain.

One factor in the amazingly low percentage of correct preoperative diagnosis in these conditions, in most hospitals, is that chronic thyroiditis is often not even mentioned as a possibility.

Even when the thyroid is exposed at the operating table, a false impression is often gained, and this may lead to unnecessary and harmful surgery.

A plea is made for the recognition of chronic thyroiditis before operation, and at operation. It is highly important for the patients that we do so.

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Dr. Samuel F. Marshall, Boston: I want to commend Dr. Patterson for the very clear clinical picture of thyroiditis. As he has stated, the disease is not common but neither is it rare, because we do see it frequently and, if we are aware of the pathologic process in the thyroid gland, I am sure we can diagnose it from a clinical standpoint many times. We have been interested in this problem, and Dr. William Meisner of Dr. Shields Warren's pathology service and myself went over our material in the Lahey Clinic, and re-examined all the tissue removed. We found, in approximately 25,000 thyroid operations, about 187 cases of thyroiditis, proven by pathologic examination. The picture is quite characteristic. As you know, the thyroid gland will react to trauma and irritation in a quite characteristic manner. The reaction, of course, may be due to irritation or to trauma, and may result in stromal changes or in epithelial changes, so that we were able to divide the 187 cases into three groups.

The first group is the infectious group in which Riedel's struma is the end stage of infection. The second group, Hashimoto's struma, struma lymphomatosa and, finally, the third group we called the non-specific group because we were not able to get sufficient characteristics to permit a more definite classification. The reaction, as I said, may be epithelial or may be stromal, and it is not uncommon to see the foreign body giant cell reaction, which is probably due to colloid spillage in this stromal tissue. We believe that the diagnosis can be established, however, in the greater percentage of cases, and we have had many more cases in which a clinical diagnosis could be made. I am not prepared to say what the number is, but it must be at least two or three times the number that were operated upon and, too, the diagnosis was faulty in that operative group, but that is easy to see inasmuch as they were operated upon because we could not definitely rule out malignancy. In 187 cases that came to surgery, in only 44 was the correct diagnosis made.

The matter of treatment is of some concern; most cases do not require surgery. If the diagnosis is established and the patient can be followed over a long period, operation is unnecessary except to rule out malignancy and to decompress the trachea because of the pressure which occurs sometimes. Dr. Lahey has described the method of removal of the thyroid isthmus over the trachea and suture of the pre-thyroid muscles to the trachea to prevent this vise-like pressure from again occurring on the trachea.

There is one point of value in surgical care of these cases. We must remember that in the infectious group, of the type that is called Riedel's in its end stages, we rarely see myxedema. We found myxedema in about 27 per cent of the cases, but in the advanced stage myxedema was present in 57 per cent. So it is important not to do a subtotal thyroidectomy on these cases, both from the standpoint of reducing the secretory epithelium and from the standpoint of the technical problems that are apt to follow attempts at removal of this very adherent gland. On the other hand, Hashimoto's can be depressed much more easily by radical removal of the gland, because practically all these cases get myxedema whether you operate upon them or not. This has been reported in other studies and was also our experience—80 per cent of our cases had myxedema. In the other group, the non-specific group, we should also avoid operation, and we noted 30 per cent myxedema in those cases. We have not used x-ray therapy, nor do we care to do so, because we want to preserve the secretory epithelium wherever possible; furthermore we want to establish the diagnosis and, again, x-ray therapy may produce more scarring and more fibrosis and make operative approach extremely difficult.

DR. F. A. BOTHE, Philadelphia: My attention has been attracted to the different colors that the types of chronic thyroiditis exhibit at the operating table. Cognizant of this fact, when we approach a very firm gland, careful hemostasis should be used so we may observe the gland's true color. My experience is confined to only 17 cases, but we have noted that the gland is a definite purplish-gray color in Hashimoto's disease, whereas it is yellowish-red in Riedel's struma. In Hashimoto's disease we have found lobulation of the gland and, in several instances, this was so pronounced that it appeared as though several lymph nodes were attached to its surface. This lobulation has not been seen in cases of Riedel's struma.

Ewing has made contribution to our knowledge of chronic thyroiditis. However, the work Graham reported in 1931 cleared up our previous misconception of thyroiditis and established struma lymphomatosa and Riedel's struma as separate and distinct types of chronic thyroiditis. Ewing believed that Riedel's struma was a later stage of Hashimoto's disease. Cases have been reported in which a second operation several years later has been performed upon patients with struma lymphomatosa and there was no change in the cellular structure of the gland from that found at the first operation; this is in keeping with Graham's viewpoint.

Lobectomy has been practiced routinely in the struma lymphomatosa cases to establish a diagnosis, rule out malignancy and to prevent subsequent tracheal obstruction. It is realized that obstructive complications are far more frequent in Riedel's struma.

One patient operated about 15 years ago has been followed very closely. A total thyroidectomy was performed, as it was impossible from a study of the frozen sections to distinguish the case from one of small round cell carcinoma. Six months later the patient developed hypoparathyroidism. Some previous writers have called attention to the fact that struma lymphomatosa may spread to the glands of internal secretion. It was felt that this complication was due to the surgical procedure; however, the fact that it did not develop until six months after operation led to the thought that this might be a case in which the disease spread to the parathyroid glands. In the past year, at the age of 82, the patient fell down two flights of stairs. She complained of severe pain in the hip and the foot on the affected side was everted. An x-ray of the hip was negative for fracture, but to our surprise the cortex of the femur had become greatly thickened even though the hypoparathyroidism had been symptomatically controlled by replacement therapy.

THE RESULTS OF A SPECIFICALLY CO-ORDINATED PLAN OF MEDICAL AND SURGICAL TREATMENT OF ESSENTIAL HYPERTENSION*

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IN 1934, BARKER AND DAVIS formulated a plan for the study of patients with essential hypertension for whom surgical therapy might be undertaken. In 1939, they reported[1] upon their clinical and experimental experiences and attempted to make clear for others the principles upon which their work was being carried out in the hope that eventually it would lend itself to comparison with that of other groups engaged in similar work.

In part, it was stated that:

> "clinically, the criteria for classifying patients as cases of essential hypertension vary considerably among various groups of workers. *Yet, before surgical procedures can be evaluated, agreement must be reached as to exactly which type of patient is being operated upon, or should be operated upon.*"
>
> "There is agreement that the clinical course of a young adult with essential hypertension may be an intense progression to a fatal termination within two years; that is, uremia and death cannot be stayed by medical treatment. On the other hand, a variable hypertension of mild degree may exist in adults under 35 years of age, which represents vasomotor instability and either requires no treatment or is controlled by simple medical measures. Late in life, a high systolic blood pressure with a normal, or nearly normal diastolic pressure, related to sclerosis of the large vessels of the body is relatively unimportant and does not require treatment."
>
> "About 90% of the mild cases of hypertension at all ages either have no symptoms or are easily relieved. Of the cases of moderately increased blood pressure, 75% either have no symptoms or can be relieved. Of the severe group of 45 years of age, many have reached a late stage in the disease after a long course. Under medical treatment, at least 30% of these patients may obtain a substantial fall in their blood pressure and another 40% may obtain symptomatic relief over long periods of time. The remaining 30% in this group have marked and irreversible vascular changes, which make amelioration of their symptoms impossible. We are confronted then with the group of young adults with malignant progression of their symptoms of hypertension and those patients with a moderate hypertension under 45 years of age for whom surgical intervention may hold hope."
>
> "Malignant hypertension is denoted by that fulminating endothelial necrotic state which may develop at any time in any hypertensive patient which usually rushes him through to an early death with evidences of widespread destruction of the vessels in the kidneys, retinae and brain.

* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

Such changes may come on suddenly in patients with severe essential hypertension resulting in terrific headaches, stupor, motor phenomena, cardiac gallop rhythm, hemorrhages from the nose and urinary tract, and actual rupture of the retinal vessels. Such a fulminating episode may be as dramatic as a fatal lobar pneumonia. However, some of the malignant cases may go on for months with periods of exacerbation and remission. Rarely, such a patient may be much improved for a long time after a coronary occlusion or a cerebral vascular accident. We have also seen a reversal from the malignant to the essential type by reducing the blood pressure and controlling it by the administration of cyanates. *This type of reversal in the phases of the hypertensive state should cause us to consider carefully surgical treatment.*"

"At which stage in the disease is surgery contraindicated and what constitutes the basic factors for such contraindications? Is it fair to require that the surgical treatment of essential hypertension be evaluated according to its effectiveness in various types and degrees of severity of the disease and the sole criterion be the effect upon the systolic blood pressure? If so, by what standards can the types and degree of severity of the disease be so classified that the results of surgical therapy in one clinic may be compared with another? One may suspect that many of the favorable surgical results reported might be duplicated by another group of workers through medical measures alone. Lowering of the diastolic pressure is a far more significant result relative to the patient's welfare than lowering of the systolic pressure. What train of physiological events results in lowering of the pressure following sympathectomy?"

We have adhered to these generally stated principles in the past 14 years and from a study of some 700 patients with essential hypertension have classified them according to therapeutic and clinical types. We do not expect complete agreement and acceptance of this classification, but it has seemed to us to be the most logical one based upon facts which can be definitely known about the patient, and to be a simple one which others can correlate with their own particular classification so that comparison of the results of surgical therapy can be made. Finally, we decided early to limit our surgical therapy to one of the types of essential hypertension and we chose that group for which medical treatment was inadequate, and progress of the disease appeared to be imminently fatal.

CLASSIFICATION OF HYPERTENSION

We believe that patients with essential hypertension can be divided clinically and therapeutically into five groups:

GROUP I—*Fluctuant:* This type represents a large proportion of the early cases of hypertension observed usually in the teens or early twenties, has often been described as adolescent hypertension, and is not associated with renal disease. It is asymptomatic and is only discovered as a result of a routine physical examination. During these early years it is impossible to tell whether the disease will remain quiescent, progress into one of the other clinical types, or in some cases disappear entirely.

As long as the etiology can not be determined, associated renal disease

is not discovered and the patient remains asymptomatic, it is questionable whether or not any therapy should be instituted. These patients uniformly respond well to thiocyanate; however, the patients are not co-operative because their early hypertension gives them so little trouble. The following case history is presented in order to show the effect of potassium thiocyanate on this type of hypertensive patient.

Case 1.—Mr. J. V., a 26-year-old white accountant, was first seen in the early part of 1947. At this time, he gave a history of asymptomatic hypertension for 5 years. He complained of nervousness and his general appearance was that of a normal person of Italian extraction. The fundi were of Grade 1 classification with only spasm and some streaking; the blood pressure was 160/100 mm. of Hg.: and no other physical abnormalities were present. Laboratory findings of the urine and blood were entirely normal and the electrocardiogram changes consisted of very minimal (less than 0.1

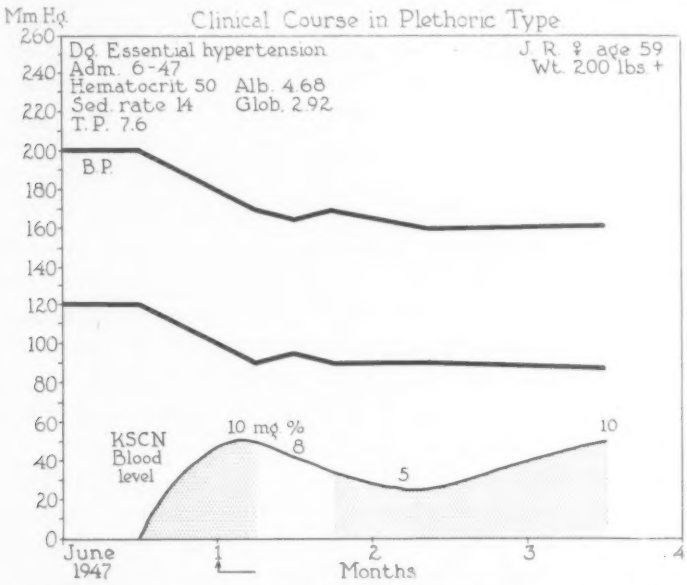

FIG. 1.—A graph showing the clinical course of a patient, the plethoric type of hypertension, showing the relationship between the blood pressure range and the blood thiocyanate level.

mm.) elevations of St segments 1 and 4. He was placed on thiocyanate therapy and in three weeks felt much more calm. His blood pressure gradually decreased until, on May 10th, it was within normal range.

On May 1, 1948, his blood pressure was 120/76 and he was taking three grains of potassium thiocyanate every other day and maintaining a blood thiocyanate level of 10 mg. per cent.

This case represents early vasospastic, or hormonal, hypertension and would probably respond best to surgical sympathectomy.

GROUP II—*Plethoric:* The plethoric hypertensive is usually a typical "businessman" with hypertension, who is energetic, active, overweight and may have distressing symptoms, particularly of headache, vertigo and angioid distress associated with a cardiovascular disturbance.

The hematocrit is usually found to be over 50% (red blood count over five million) and the sedimentation rate 1 to 5 mm. or less in one hour. We are in the habit of describing this blood as viscid or "sticky", and in such cases, cerebral or coronary thromboses are common.

Provided that the patients do not have associated irreversible renal disease, continued control of blood cyanate concentration will result in a rather prompt relief of the hypertensive symptoms and a gradual diminution in, first, the systolic, and later, the diastolic pressure. It is dangerous to drop these patients' pressures rapidly; therefore, the early dosage of the cyanates should be small and gradually increased as renal thiocyanate clearance improves. Often these patients have a rapid renal clearance of thiocyanate and may require as much as 20 gr. of the drug daily to maintain an adequate blood concentration.

During the first few months of treatment, the hematocrit will drop to 45 or less and the sedimentation rate will increase 10 or 15 mm. in an hour, which represents a definite change in the hemogram resulting from a thiocyanate effect on the red blood count and therefore on blood viscosity.

These patients represent the most favorable group for treatment with thiocyanates and can be best illustrated not only by the case history which follows, but also by a line graph (Fig. 1) which illustrates the effect of thiocyanate on the blood pressure and hemogram in this type of individual.

Case 2.—Mr. J. R. a 59-year-old white man, was first seen in late June, 1947, complaining of shortness of breath on exertion, a buzzing in his head in the daytime and nocturia. He said that his blood pressure had been high as long as he could remember and that in 1946, he had had some heart failure and had been required to spend two months in bed. A laboratory survey showed a sedimentation rate 5; hematocrit 50; total protein 7.6; albumen 4.68; globulin 2.92; blood urea nitrogen 12.6; and uric acid, 5.2. The electrocardiogram demonstrated the presence of a first degree heart block.

On physical examination his fundi were of Class 2 severity, and aside from a plethoric stocky appearance and a blood pressure of 220/120, there were no significant findings.

He was placed on thiocyanate therapy and in two weeks he had a blood cyanate level of 10 associated with a fall of pressure to 170/90. Blood pressures and thiocyanate levels have been at this level or lower for ten months and the cardiogram shows a diminution in the PR interval of .02 and there is no deformity of a recent coronary occlusion. His sedimentation rate is now 15 mm. in one hour and the hematocrit is 47%. He has had no hypertensive symptoms since his blood pressure has dropped to the lower levels.

GROUP III—*Menopausal* hypertension is one of the most frequent types of hypertension seen in the female and corresponds in many respects to the plethoric type of hypertension in the male. It is usually accompanied by numerous and severe symptoms of hypertension which are superimposed upon those that are often associated with the menopause. Unlike the plethoric type of hypertension, however, a high hematocrit and low sedimentation rate are not often seen. The blood cholesterol is likely to be elevated.

The hypertensive, as well as the menopausal symptoms, can often be controlled by estrogenic therapy and sedation alone, but the blood pressure which is not affected by these measures will often respond to thiocyanate therapy.

By the above description we do not wish to infer that menopause in itself is a cause of essential hypertension. It most likely is not. However, menopause does exaggerate the symptoms of a pre-existing, or coincidental, hypertension in patients with only a moderate elevation of the blood pressure. There may be a wide fluctuation in the blood pressure readings in the level type, or a pre-existing diastolic fixed type of blood pressure may be seriously aggravated, so that a clinical classification is made easily and the therapeutic approach to the problem is well defined. It has long been observed that if the patient can be brought safely through her period of menopause, be it 5 or 15 years, the hypertension will subsequently burn itself out.

Case 3.—Mrs. M. W., a 50-year-old white female, was first seen in March, 1947. She complained of severe hot flashes and nervousness for two years with increasing frequency. Just prior to this time, she had some exertional dyspnea, orthopnea, and occipital headaches associated with a blood pressure 210/110. A survey of her status at this time demonstrated no cardiac enlargement, normal urine and normal hemogram.

She was placed on estrogenic substances by mouth with the result there was a marked sympomatic improvement. She was studied further and was found to have normal renalfunction and metabolism rate. The electrocardiogram was normal.

Thiocyanate therapy was started, and one month later when a therapeutic blood level had been reached, the arterial tension was 190/96. These levels were maintained in the next three months; the usual level of arterial tension was around 154/86 and she was asymptomatic.

To ascertain the effect of thiocyanate better, this medication was stopped but the estrogenic substances continued. In the succeeding two months, the blood pressure rose to levels of 190/100. Roentgenogram of her urinary system at this time was entirely normal and no abnormality of the serum proteins was manifest. Thiocyanates were again started with a good therapeutic effect.

GROUP IV—The *high diastolic* type of essential hypertension as seen in the *male,* most often between the ages of 35 and 50, represents the most severe type of essential hypertension with which we have had to deal. This is indicative of either a pre-malignant phase of hypertension, or a rapidly progressive type of essential hypertension with the occurrence of heart failure, or a cerebral vascular accident, within a five year period. Unlike the female in this same age group with a severe high diastolic pressure, the male does not tolerate an increased blood pressure for a very long period of time. These patients do not respond well to thiocyanate therapy except for relatively short periods of time, and if they do show some blood pressure lability and some response to thiocyanate therapy, though it is temporary, we have subjected them to sympathectomy before the onset of renal and cardiac failure, or malignant hypertension.

Case 4.—Mr. B. K., at the age of 47, was admitted to the hospital in November, 1946. His family was free from hypertensive disease. Nocturia 3 to 4 times was pres-

ent almost an entire lifetime. In January, 1946, hypertension was found and was associated with frontal and coronal headaches of moderate severity. In May, 1946, the evening hours were marked by asthma. In the following month ankle edema was present, and in October, 1946, exertional dypsnea and orthopnea were of moderate severity.

The average blood pressure was 200/130 and was associated with the classical signs of heart failure. The retinal findings were classified as Gifford III. The hemogram demonstrated moderate hemodilution. There was moderately reduced renal function as demonstrated by the commonly employed tests and "heart-failure" urine. The electrocardiogram demonstrated a left ventricular strain pattern. Culture of the urine was negative. A standard roentgenray of the chest showed an aortic configuration of the heart with 20% enlargement. The patient's heart failure was treated in a routine manner with a reduction of the signs and symptoms of congestion. Commonly employed vasolability tests demonstrated that the blood pressure was labile; the sleeping blood pressure 155/90.

The patient was discharged from the hospital but the symptoms continued so he again was admitted for the consideration of surgical treatment. Inasmuch as all previous therapeutic attempts, including thiocyanates, had been futile, sympathectomy was advised and carried out in January 1947. A moderate amount of arteriolonephrosclerosis and slight tubular atrophy were apparent in a biopsy specimen. One month following surgery the blood pressure returned to the preoperative levels. In the third postoperative month, standing produced a diastolic rise in pressure and at the end of five minutes it was 210/140. During this time it was necessary to continue therapy for congestive heart failure and despite this in the 5th postoperative month frank decompensation was again noted. Thiocyanates were again administered and after three months the patient was able to resume 8 hours of reduced work. At this time the blood pressure ranged around 215/115. The roentgen ray showed 25% cardiac enlargement. However, the renal function tests were somewhat improved. Thiocyanates were continued at levels of 10 mg. %. In April, 1948, 14 months after surgery, frank congestion again became notable. The blood pressure ranged about 210/132 and with the aid of mercurial diuretics the patient was able to continue light work, though obviously handicapped. He was, nevertheless, in remarkably good health, considering the gravity of his initial disease.

GROUP IV B—The *high diastolic* type of hypertension in the *female*, most often observed between the ages of 25 and 40, and exclusive of those cases of hypertension which are complications of pregnancy, also represent a severe type of hypertension. However, the female hypertensive in this group, unlike the male, is much better able to withstand this severe degree of hypertension and the disease apparently progresses much more slowly. They are likely to have severe symptoms associated with the disease, which may be alleviated temporarily by the use of thiocyanates.

These patients are also of the type that are recommended for surgical sympathectomy in order to prevent, if possible, the onset of left ventricular failure.

Case 5.—Mrs. D. G. a 41-year-old white woman of Spanish extraction, was first seen about thirteen years ago. At this time, she stated that her hypertension had been found five years previously, at the age of 24. When she was 26, she had some ankle edema, and two years subsequently symptoms of headache, weakness, dyspnea, nocturnal dyspnea, palpitation and insomnia were associated with blood pressures around 220/130 mm. of Hg.

In 1935, she was admitted to the hospital because of the advent of early left heart failure. Left ventricular hypertrophy and a moderate secondary anemia were found at this time. The symptoms became so severe and unalterable under medical therapy that the splanchnic nerves and 10th, 11th and 12th thoracic sympathetic ganglia and the intervening trunks were removed bilaterally in 1935. Since this time, she has been on thiocyanate treatment and has consistently run much lower blood pressures, ranging between 175 and 200 mm. of Hg. systolic (230 occasionally) and 100 and 115 mm. of Hg. diastolic (130 rarely). She has had occasional mild signs and symptoms of heart failure associated with moderate nervous tension responding well to the usual forms of therapy. She now has considerable aortic sclerosis with no appreciable change in heart size; it still is approximately 15% enlarged. Likewise, all other signs and symptoms have not changed appreciably in these 13 years, and she is able to carry on full time duties in the business world and at home. She repeatedly states that she feels very much better and would be unable to carry on without thiocyanate treatment.

GROUP V—The *arteriosclerotic hypertensive,* usually seen in its early phases between the ages of 50 and 60, is characterized by relatively high systolic and relatively low diastolic blood pressure readings. Its course well represents the prolonged benign nature of some cases of hypertension, and although it is often accompanied by cerebral symptoms of headache, vertigo, tinnitus, and even symptoms of left ventricular failure, the disease itself is not severe and is compatible with a relatively long and useful life.

Some cases respond very well to small doses of thiocyanate but should be observed very carefully in order to avoid rapid drops in blood pressure. Other cases do not respond to thiocyanate treatment, nevertheless, the benign course of the disease is well illustrated by the following case history. Here again, however, a benign course is more likely in the female than in the male.

Case 6.—Mrs. R. T., a 75-year-old colored woman, formerly obese, was first seen 20 years ago with a moderate systolic elevation of arterial tension (BP 162/80). She complained of many bizarre symptoms which included palpitation, weakness, occasional dizziness, shortness of breath, and occipital headache. The general trend of arterial tension was upward with a greater rise of the systolic pressure. Three years later the average tension was 170/100mm. of Hg. and in another five years, the average tension was about 186/100, although occasional readings of 225/110 were recorded. Renal function tests were always normal.

About this time, diabetes was discovered and she was placed on a rigid diet which was also designed to bring about weight reduction. Still two years later her tension was about 200/93. She was given a trial on thiocyanate therapy. When adequate blood levels were maintained, her arterial tension was consistently about 165/86. She failed to follow therapeutic directions so this medication was discontinued

From that time until the present (10 years), the patient has had to a greater or lesser degree both right and left heart failure associated with levels of arterial tension similar to those prior to the thiocyanate therapy. The usual therapeutic agents have been employed and include aminophyllin, phenobarbital and salyrgen, (92 injections). In 1947, however, occasional systolic readings of 240 were observed. Blood chemistries remain essentially normal, the roentgenray of the heart shows 15% enlargement and marked sclerosis and tortuosity of the aorta.

GROUP VI—*Malignant hypertension* is characterized by severe hyper-

tensive symptoms, including convulsions and coma. It may occur in any age group and its clinical course is rapidly progressive to a fatality. It manifests itself by a severe, progressive, generalized necrotizing arteriolar disease and renal failure. The disease shows no response to thiocyanate or any

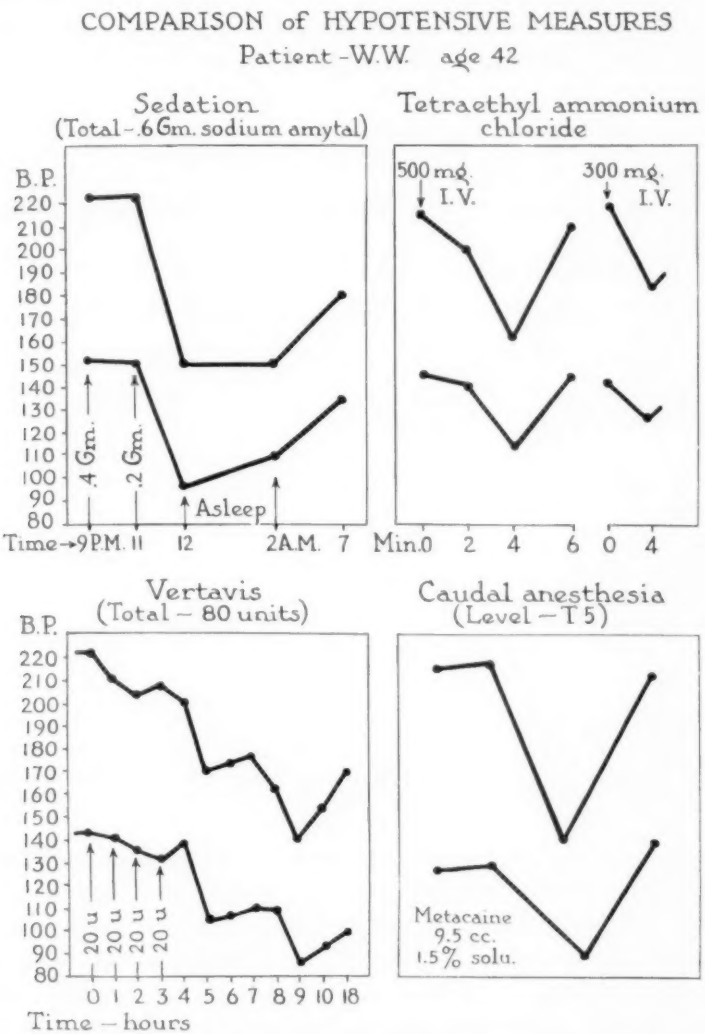

FIG. 2.—A comparison of hypotensive tests used preoperatively in patient W. W., who had high diastolic type of hypertension.

other medicinal type of therapy. A patient with any one of the types of hypertension described above may suddenly enter the malignant phase of essential hypertension and this occurrence is unpredictable and most likely to happen in the high diastolic group. Of course, a patient may be observed for the first time with the malignant type of hypertenson and evidence may be un-

available that previously the symptoms of any other type of hypertension were present.

Recent reports (*2*, *3*) seem to indicate that the rapid progress of the disease may be slowed temporarily and the life of patients with malignant hypertension may be prolonged somewhat by sympathectomy. However, there is a high operative risk in these patients and it has been our experience that immediate postoperative vascular accidents are the most common cause of death.

Choice of Cases for Surgical Treatment

We chose cases from the group of patients whom we classified as belonging to *high diastolic type* of hypertension. We further restricted our

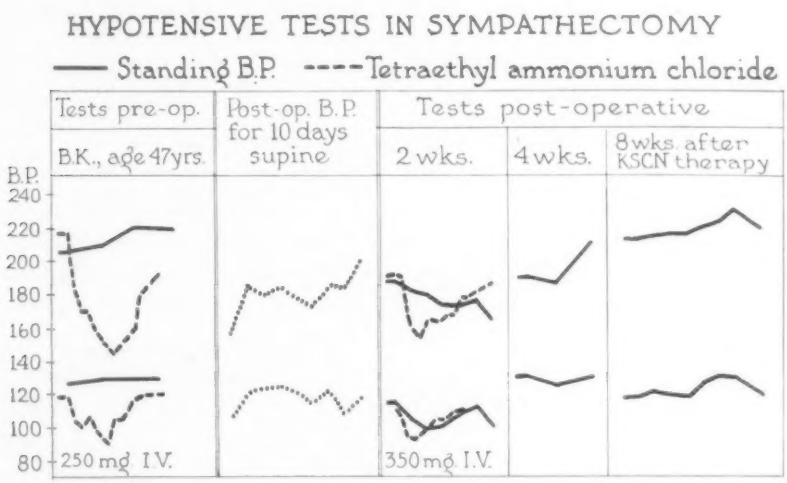

Fig. 3.—A graph showing comparison between standing blood pressures and the effect of tetraethyl ammonium chloride pre- and postoperatively on patient B. K., who had high diastolic type of pressure.

choice to those in this group who had been given an adequate and thorough trial of therapy with the thiocyanates and had proven to be resistant to this drug. That is to say, their diastolic and systolic pressures and their symptoms could not be improved by cyanate blood levels below those which produced toxic symptoms.

A third indication for the choice of patients was that they should have a labile blood pressure as evidenced by a group of pressor and depressor tests. General considerations upon which we based our surgical indications were that the patients should have systolic blood pressures over 200 and diastolic pressures over 100 mms. of mercury; that there be no evidence of chronic glomerulonephritis or pyelonephritis; no significant peripheral vascular sclerosis and that the clinical course be shown to be progressive, but not entering the malignant phase of hypertension. The average age of the patients operated upon was 40.08 years with a mean age of 39 years.

Pressor and Depressor Tests. We have used sodium amytal, sodium pentothal, caudal anesthesia, induced hyperpnea, tetraethyl ammonium bromide and vertavis as vasorelaxor tests, and the cold pressor tests and the administration of carbon dioxide as vasopressor indicators.

We have noted repeatedly that the most significant fall in blood pressure with caudal anesthesia occurs only when the level of anesthesia reaches the thoracic fifth dermatome. The specificity of this level in our experience is very significant and definite.

All of the patients in the high diastolic group upon whom we operated showed satisfactory responses to all the vasorelaxor and vasopressor tests used, but none of the tests gave any information whatever of the character

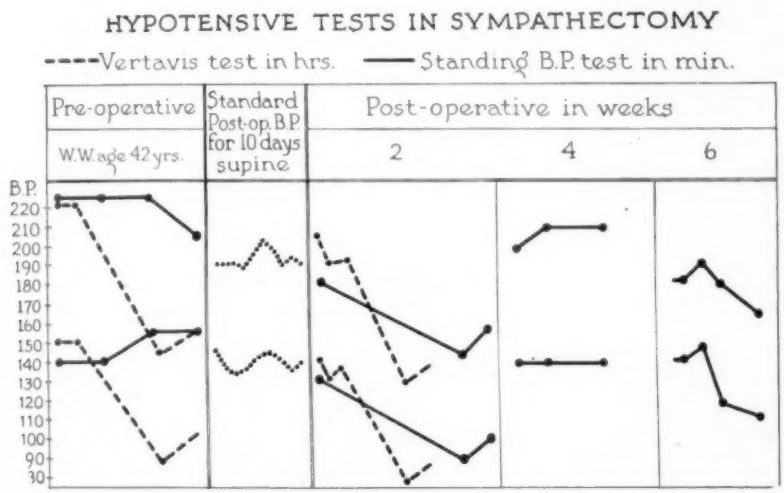

FIG. 4.—A comparison of standing blood pressure and the Vertavis test pre- and post-operatively on patient W. W., who had high diastolic type of hypertension.

or extent of the response we might expect after sympathectomy. In only two of the patients operated upon have we observed significant changes in the blood pressure readings with change of posture following sympathectomy, although in other patients the extent of the operation was identical. Figure 2 shows a comparison of hypotensive tests used preoperatively in patient W. W. From these tests alone, one could only conclude that this patient would have a satisfactory response following sympathectomy. As a matter of fact, the patient was operated upon in February; was discharged from the hospital, and in April of the same year, showed signs of a left ventricular insufficiency, complained of nocturnal dyspnea and developed a pulsus alternans. These symptoms finally culminated in a congestive heart failure which terminated fatally in October, eight months after operation. Figure 3 shows the comparison between the standing blood pressures before operation and two weeks, four weeks, and eight weeks after operation in patient

B. K. who had high diastolic type of hypertension. It also shows the blood pressure taken in the supine position ten days postoperatively. A comparison between the intravenous injection of 250 mgs. of tetraethyl ammonium chloride preoperatively and two weeks postoperatively can be compared with the intravenous injection of 350 mgs. of the same drug two weeks postoperatively. Figure 4 shows a comparison between the standing blood pressure pre-and postoperatively and the administration of Vertavis preoperatively and two weeks postoperatively on patient W. W. who had high diastolic type of hypertension. This patient's postoperative blood pressure in the supine position is also illustrated.

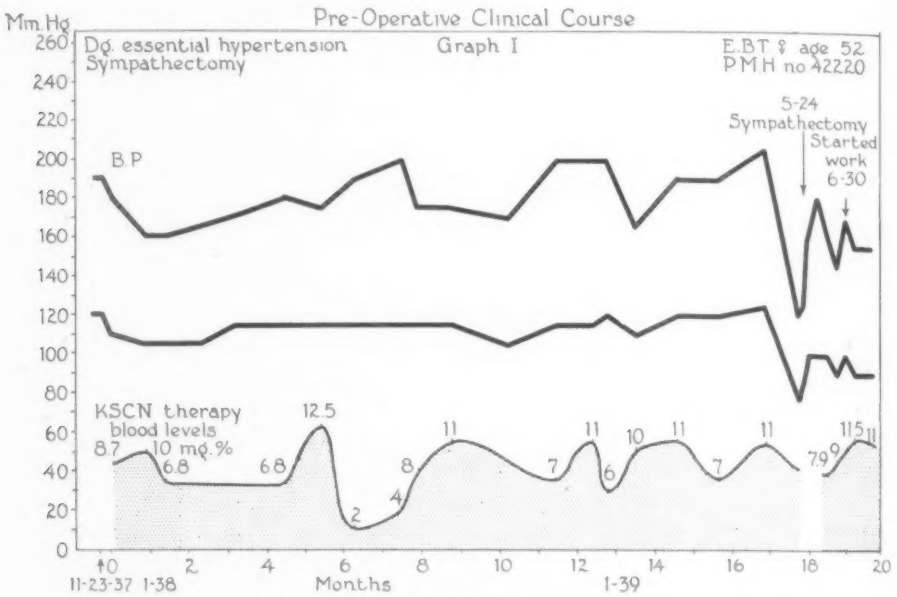

FIG. 5.—Graph 1—pre-operative clinical course on patient E. B. T. (high diastolic hypertension).

Surgical Procedures and Results

This report concerns 25 patients with the high diastolic type of hypertension, who have been followed pre- and postoperatively for a sufficiently long period of time to allow us to arrive at definite opinions about them. Thirteen of these patients had supradiaphragmatic removal of the thoracic sympathetic ganglia and chains from thoracic ninth to twelfth inclusive, and the splanchnic nerves, bilaterally. Two patients had supra- and infradiaphragmatic removal of the thoracic sympathetic ganglia and chains from the ninth to the twelfth inclusive; the lumbar sympathetic ganglia and chains from lumbar one to lumbar two inclusive, and the splanchnic nerves, bilaterally. Nine patients had supra- and infradiaphragmatic removal of the thoracic ganglia and chains from the sixth to the twelfth inclusive; lumbar one, two and three ganglia and intervening chains and the splanchnics,

bilaterally. One patient had an infradiaphragmatic removal of lumbar one, two and three ganglia and the intervening chain, bilaterally.

None of the patients in this group showed satisfactory lowering of the systolic and diastolic blood pressures, or improvements in their symptoms following operation alone, which would allow them to resume their former social and economic positions. The most significant result, however, has been that whereas all of the patients have been resistant to cyanate therapy prior to operation, following sympathectomy they have become cyanate sensitive to the extent that their symptoms and blood pressure levels have been improved by the maintenance of cyanate blood levels well below those which produce toxic symptoms.

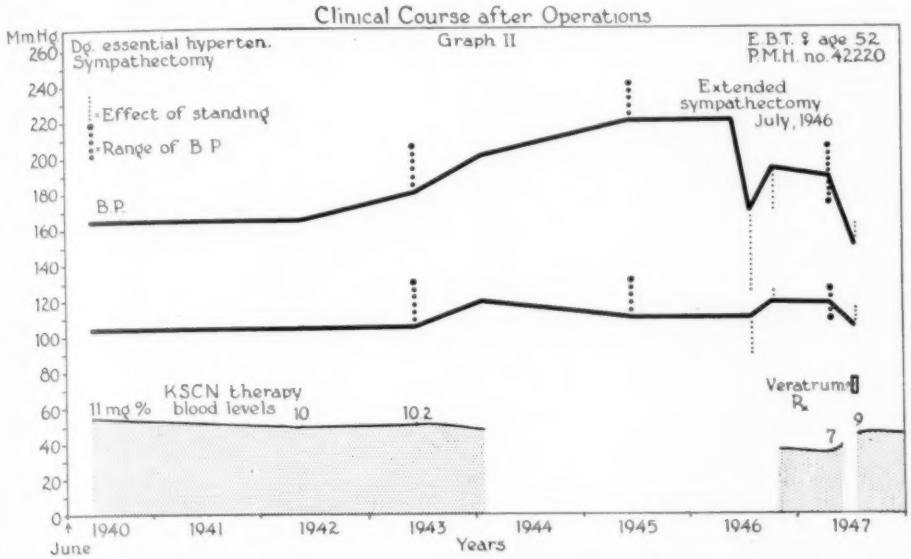

FIG. 5.—Graph 2—clinical course of patient E. B. T. (high diastolic hypertension) after first sympathectomy and extended sympathectomy.

Twelve patients in this group have died since operation so that the progression of their disease was not halted by either surgical or medical therapy. Eight of these twelve patients died within two years following sympathectomy. Four of the 12 deaths occurred immediately, during hospitalization for surgery, from heart failure and intraventricular hemorrhage.

Of the remaining 13 patients operated upon, four had their sympathectomies less than two years ago. Seven are actively engaged in their former social and economic positions and are upon cyanate therapy with excellent results. One of these patients was operated upon 13 years ago, and is actively engaged in her household and other activities with a blood cyanate level which averages about 6 mgms. percent. Before operation, her symptoms and blood pressure levels could not be controlled even with high cyanate blood levels which invariably produced marked toxic symptoms of the drug.

One other patient of this group of 13 has recurrent episodes of encephalopathy with unconsciousness; another has recently left the hospital after recovering from severe left and less severe right ventricular heart failure symptoms, and four are not actively returned to their former occupations, but are symptomatically improved. There is no doubt that the postoperative results in the high diastolic group of patients have been far better among women than men, which only re-emphasizes our original statement that

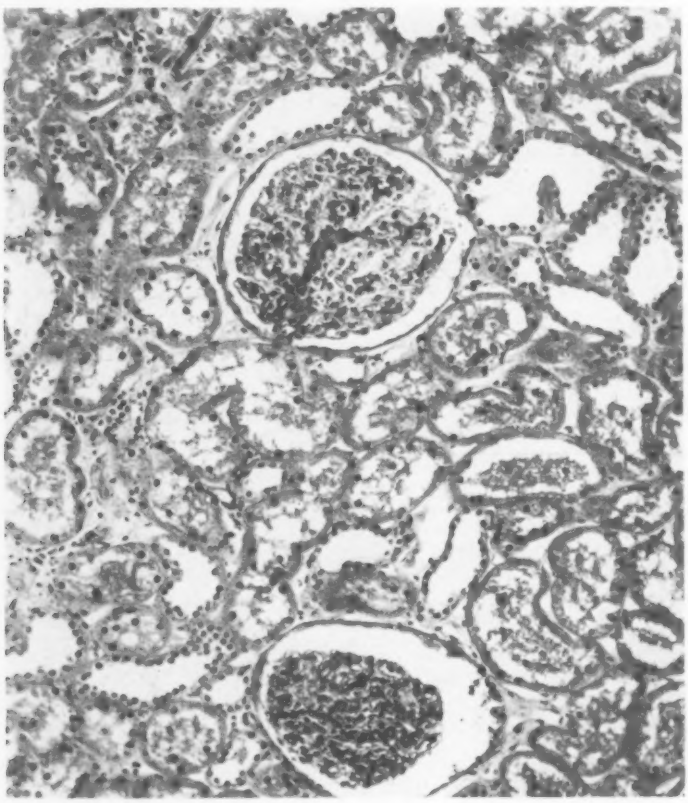

FIG. 6.—Male patient with severe hypertension, high diastolic type, with very few sclerotic changes in the terminal arterioles.

women withstand this type of hypertension better than men, but for what reason we do not know.

The following summary of the circumstances in the case of Mr. E. B. T., who was 52 years of age at the time of his operation, illustrates the results of sympathectomy in this type of hypertension:

Case 7.—Mr. E. B. T., aged 52 years, first came under observation in November, 1937, when his blood pressure was 190/120 mms. Hg. and he complained of the usual symptoms of headache, irritability, dyspnea and fatigue. He was placed on potassium thiocyanate and was so treated until May of 1939. During that time, his cyanate blood levels could be raised to 12.5 mg. % before toxic symptoms of the drug developed.

However, his diastolic blood pressure never fell below 100 mms. Hg., and his systolic pressure ranged from 160 to 200 mms. Hg.

In May of 1939, the thoracic ganglia and chain were removed bilaterally from thoracic ninth to twelfth inclusive, and the splanchnic nerves were resected.

The patient returned to his work in June of 1939 and was maintained on cyanates and with blood pressures averaging 160 systolic and 100 diastolic. In 1943, his blood pressure readings began to rise following cessation of thiocyanate therapy and in 1946 the systolic pressure reached 220 and the diastolic remained at 100. He was operated upon again in July of 1946 at another hospital where the lumbar ganglia and chains were removed and the thoracic chains removed with the ganglia up to thoracic

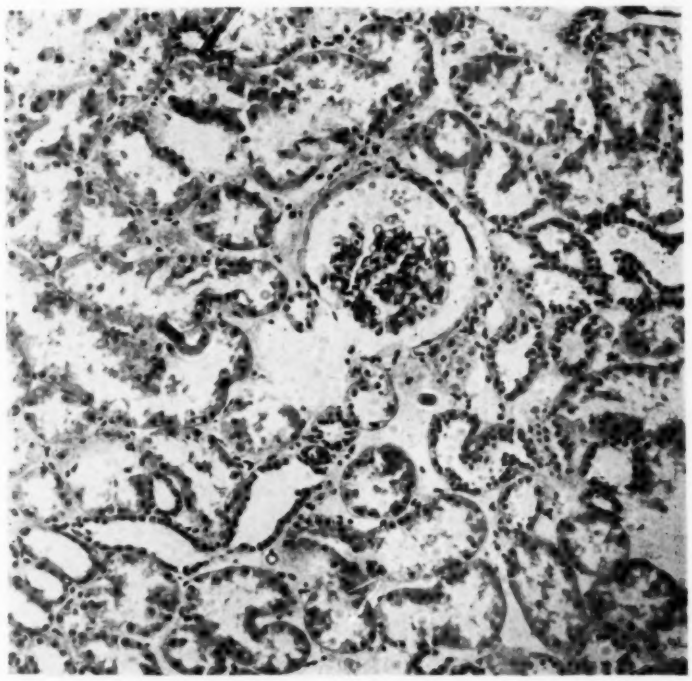

FIG. 7.—Female patient with moderate hypertension of the high diastolic type, with extensive sclerosis in the arterioles.

fifth bilaterally. Following this operation, this patient showed a definite postural hypotension. He was placed upon veratrum therapy and shows lower blood pressure levels, particularly the systolic reading which has been recorded as low as 140 mms. This may possibly be the first indication of impending congestive heart failure. However, he now shows a reversal of his blood pressure levels upon standing and both the systolic and diastolic readings are higher upon standing than when lying. (Fig. 5)

We have previously reported that we have been able experimentally in dogs and monkeys to produce hypertension by the Goldblatt clamp and by wrapping the kidneys in silk, which responds to the administration of the thiocyanates exactly as do hypertensive symptoms in man. We have been unable as yet to explain the site or nature of the effect of the thiocyanates,

nor why this group of patients resistant to the drug before operation, become sensitive to the cyanates following sympathectomy.

Biopsy Specimens of Kidneys

We have taken specimens of the kidneys at the time of operation and have examined the kidneys microscopically after autopsy in an effort to correlate the clinical symptoms and course with the pathological changes in

Fig. 8.—Male patient with hypertension of the high diastolic type with low grade sclerotic changes in the arterioles and sclerosis in the arteries.

the kidneys in an effort to draw the indications for surgical therapy more accurately.

Figure 6 is a microphotograph of a specimen of the kidney of a patient who clinically had a very severe hypertension of the high diastolic type. One must look very carefully to find any sclerotic changes in the terminal arterioles. Figure 7 is a microphotograph of a specimen of the kidney of

a patient who had the symptoms of what was judged to be clinically a moderate hypertension. Yet, the sections of her kidney show a rather extensive sclerosis in the arterioles. This patient is one of the best of the postoperative results following sympathectomy.

We have been unable to find any correlation of the pathological changes in the kidney and the function in these cases of hypertension which would be useful in choosing those patients unsuitable for surgical treatment. Arterial sclerosis in the kidney may come with age alone. It is the combination of arteriolar and arterial sclerosis which is pertinent in the cases of hypertension. Evidence of arteriolar sclerosis may be very hard to find in the specimens removed for study, or it maybe quite evident, irrespective of the severity or mildness of the clinical symptoms and course. Arterial sclerosis without arteriolar sclerosis may be present in hypertension but not arteriolar without arterial sclerosis. Figure 8 is a microphotograph of a kidney specimen from a patient with a clinical high grade hypertension of the high diastolic type. The changes in the arterioles are present but low grade in extent and the arteries show sclerosis.

SUMMARY

1. Sympathectomy alone has not been successful in permanently reducing the blood pressure levels in the high diastolic type of hypertension regardless of the extent of the operation. However, in some cases the subjective symptoms have been improved temporarily although the clinical course of the disease has remained unchanged.

2. Sympathectomy has caused patients in this group who have been resistant to thiocyanate therapy preoperatively to become sensitive to the administration of this drug. This result has been confirmed by laboratory experiments upon monkeys and dogs. The physiological explanation for this effect has not as yet been explained to our satisfaction.

3. There has been no significant change in the blood pressure levels, or heart size, unless the patients of this group have been given thiocyanates postoperatively.

4. In the high diastolic type of hypertension vasopressor or vasorelaxor tests have not proven to be sufficiently accurate to say exactly which of these patients should be operated upon.

5. The medical management of patients of this group, particularly with the administration of thiocyanates properly controlled, is good in the early stages of the disease, but sooner or later all have become resistant to this drug.

6. We believe that the results of surgical therapy in patients with hypertension can be evaluated only by a comparison with specific groups of patients belonging to types of hypertension based upon their clinical symptoms and course. Those types of hypertension which have been shown to respond well to medical management, we believe, will show good results

from surgical therapy alone, but the selection of patients for operation should be made, not upon blood pressure ranges alone, but upon the characteristic symptoms and clinical course of the disease. Until comparison of the results of surgical therapy is made upon accepted classifications of the clinical symptoms and course of this disease, confusion in interpretation of the surgical results will exist.

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GANGLIOSYMPATHECTOMY AND BILATERAL HEMIADRENALECTOMY FOR SEVEREST GRADE OF HYPERTENSION*

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BECAUSE RESULTS ARE OFTEN UNPREDICTABLE, uncertain, and transitory, sympathectomy is not generally advocated for the severest grades of hypertension. I began to add various procedures to the customary dorsolumbar operation about seven years ago in the hope of improving the result in such cases. They consisted of denervation of the adrenal glands, stripping of the adventitia of the lower thoracic aorta, and subtotal removal of the semilunar ganglia. Finally all were employed without any consistent improvement in results.

The addition of procedures on the adrenals was then undertaken. One adrenal was removed in each of a few cases, apparently without effect. The next procedure, was employed in only one case, excision of half of one adrenal and complete removal of the opposite one at the second stage sympathectomy. The procedure proved to be too drastic possibly because of contralateral hemorrhage which has been noted to occur experimentally. A profound drop in blood pressure was combatted for several weeks by heroic measures. An adrenal transplant was without definitive effect and the frequent administration of cortex has been required in order to maintain a systolic pressure between 110 and 120. An Addisonian symptom-complex, including pigmentation, has developed. The case is possibly unique insofar as the cure of hypertension is concerned but at the expense of what appears to be permanent adrenal insufficiency.

Subsequent operations, now 14 in number, consisted of the removal of approximately the upper half of each adrenal gland at the time of sympathectomy. The operative procedure can be outlined briefly. Under intratracheal anesthesia the entire twelfth rib and usually a substantial paravertebral section of the eleventh are removed. The thoracic dissection is extrapleural. The sympathetic trunk is divided at the level of the fourth or fifth ribs and is freed to the diaphragm. The splanchnic is similarly treated, the thoracic aorta being exposed in this step. The adventitia of the lower thoracic aorta, which bears sympathetic fibers, is freed and excised down to the diaphragm. The latter is severed locally to the region of exit of the sympathetic nerves into the retroperitoneal space, in order to simplify their further dissection and to aid in some measure in the exposure of the adrenal. The greater splanchnic is dissected to the semilunar ganglion which is excised almost to the aorta. The sympathetic trunk is freed to the second lumbar ganglion below which it is removed. The adrenal gland, previously inspected to ascertain if it were the seat of a neoplasm, now is brought into

* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

full view by suitable retractors and the removal of overlying fat (when present). The upper half is dissected free with meticulous attention to hemostasis. In order to remove the upper half without hemorrhage chain sutures are passed and tied gently and the adrenal detached step by step beyond the line of sutures. The result usually has been the removal of somewhat more than half the adrenal. However the main blood supply which enters the lower half remains intact. Virtually the same operative procedure on both adrenals, in addition to bilateral sympathectomy, semilunar ganglionectomy and stripping of the adventitia of the aorta, was performed in each of the 14 patients.

A brief reference should be made to the types of operative cases before mention is made of the results of operation. The preponderance of the patients suffered from the severest forms of hypertension with systolic ranges from 250 to 300, diastolic from 150 to 190. A number were in the older age group. The first operation having been performed less than three years ago, reference can be made to interval results alone. There has been no mortality and but little morbidity. The low morbidity is ascribable to the fact that the pleura is rarely entered and if entered sutured, and the trapped air withdrawn at the end of operation.

There was one failure to influence the blood pressure. This was the only case in which microscopic examination of the removed adrenal revealed generalized arteriosclerosis. In addition to the usual symptomatic relief, the result of operation in 13 cases has been a pronounced reduction in blood pressure, below the 200 systolic level in most instances, with proportionate reduction in the diastolic level. Lability of blood pressure has been evident in more than half the cases. However, the striking feature has been a persistent, pronounced, but nevertheless symptom-free postural hypotension. A drop from 180 to 130 noted a year or more after operation has not been unusual.

Bilateral hemiadrenalectomy was employed in three cases of severe hypertension after sympathectomy had failed, with pronounced improvement in two and little improvement in one. Hemiadrenalectomy, performed on one side in three cases, was not attempted on the other because too great a reduction in blood pressure was feared at the time of completion of the sympathectomy on the second side. The results were satisfactory in these three cases but they did not belong to the severest grades of hypertension. However, the uncertain results obtained in severe hypertension raise the question of the addition of unilateral or even bilateral hemiadrenalectomy in cases short of the most severe forms of hypertension. Finally, the influence of bilateral hemiadrenalectomy on blood pressure appears to be so salutary as well as distinctive that the question of employing this procedure alone for hypertension naturally arises. Theoretically at any rate, subtotal adrenalectomy for hypertension appears to parallel subtotal thyroidectomy for Graves's Disease.

DISCUSSION.—DR. A. W. ADSON, Rochester, Minn.: I have enjoyed these papers and commend Dr. Davis for his conservative attitude in employing extensive splanchnic nerve resections in the treatment of hypertension. Our experience corroborates Dr. Davis' report in that the administration of cyanates often is more effective in lowering blood pressures following splanchnic rescetions than they were when administered prior to surgery.

The reports of Crile and DeCorsey prompted me to resect one-half of each adrenal gland at the time of operation when I resected the splanchnic nerves, a portion of the celiac ganglion and the upper two lumbar sympathetic ganglia in 25 consecutive cases. The postoperative results in those patients appeared to be no different than those obtained from the extensive sympathectomies. Our observations probably were very similar to those reported by Dr. Neuhof.

As many of you know, we at the Mayo Clinic have been interested in controlling essential hypertension by operative procedures on the sympathetic nervous system. In 1930, while observing the blood pressures fall in a patient who had been given a spinal anesthetic for a pelvic operation, it occurred to me that a bilateral rhizotomy of the anterior roots of the spinal nerves from the sixth dorsal to the second lumbar inclusive should produce similar falls in blood pressures to those that resulted from the spinal anesthetic, since the white sympathetic rami carrying vasoconstrictor impulses would be interrupted and paralyzed just as they were during the spinal anesthetic. The operation, a laminectomy and rhizotomy, was employed in 30 cases. It was discontinued because of its magnitude and the surgical shock that resulted from the marked hypotension. The subdiaphragmatic approach was substituted for the laminectomy and rhizotomy.

The subdiaphragmatic approach through the loin was extraperitoneal. The kidney and liver were retracted mesially with a broad illuminated retractor which readily exposed the splanchnic nerves, the celiac ganglion and the upper portion of the sympathetic lumbar chain including the first and second lumbar ganglia. The splanchnic trunks were resected as was a portion of the celiac ganglion and the upper lumbar chain. The immediate effect was a marked hypotension. The late results showed that about one-third of the patients remained well. They were free from symptoms and blood pressures remained within normal levels. One-third of the patients developed a gradual rise of blood pressures within two to four years but still were free of symptoms. The last one-third of the postoperative group responded less favorably. Blood pressures and symptoms returned to preoperative levels within six to 12 months.

In view of the fact that other operations such as resection of the splanchnic trunks by the supradiaphragmatic approach and by the thoracolumbar approach which includes a portion of the celiac ganglion and the upper lumbar chain, we, the neurosurgeons at the Mayo Clinic are employing the different operative procedures in order to compare the effectiveness of each. At present, it appears that the late results following surgery are very similar regardless of the technic employed.

Since Dr. Crile in treating hypertension may not have completely removed the celiac ganglion by the tactile and avulsion method, and in the light of the investigative work on vasospasm of renal arteries in shock by Trueta and collaborators, I have resected the celiac ganglion under direct vision, making sure to include the aorticorenal ganglion, for essential hypertension. The object of this radical resection is to also interrupt the postganglionic sympathetic fibers to the adrenal glands and kidneys. The immediate postoperative hypotension is as marked as it was following the extensive rhizotomy. The postoperative shock is much less than the shock and sequela following thoracolumbar procedure.

I still am not too thoroughly convinced that regeneration of sympathetic fibers takes place, and this is especially so if a gap of three centimeters is left between the severed ends. As a matter of routine, I usually apply a silver clip on the sectioned

ends of the sympathetic nerves or trunks to control any bleeding that might take place. However, the silver clip may have taken on a more significant role since a silver sulfide develops in the vicinity of the clip, which destroys and fixes neurogenic tissue. The lantern slide of such a specimen illustrates the point. The two specimens on the slide are from a patient upon whom I had operated ten years previously for hypertension, by the subdiaphragmatic method. At that time, I applied a silver clip on the proximal ends of the splanchnic trunks. Since this patient's blood pressures gradually rose to preoperative levels, Dr. Craig advised that another operation be done, and he removed the thoracic portion of the splanchnic trunks. As you observe, the lower end of the specimen is black in appearance, a portion of silver clip still remains, the neuroma consists chiefly of fibrous tissue, and there is no evidence of regeneration.

I still believe that our greatest problem in attempting to manage the treatment of essential hypertension is to select the patient for the particular type of treatment, whether it be medical or surgical treatment. If it is to be surgical treatment, employ it before irreversible changes have taken place in the cardio-renal-vascular mechanism.

MANAGEMENT OF MASSIVELY BLEEDING PEPTIC ULCER*

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OPINION CONTINUES TO BE DIVIDED on the management of gross bleeding from peptic ulcer, even though clinical experience is distressingly ample in most large teaching hospitals. Reasons for confusion of thought evident in the literature of the subject are lack of precise clinical observations and careful reporting, lack of definite criteria in the selection of cases to be treated in any particular manner, variation in the quality of medical or surgical care provided, and what may be called clinical bias. Various authors have focused attention on the life-saving value of early surgical control of hemorrhage in these cases, but the ideas developed in their pioneer work have not as yet won the enthusiastic support of gastroenterologists 1-9.

It has seemed to us that advances in surgical technic and care, improvements in anesthesia, and sounder knowledge of hemorrhagic shock and its treatment[10 11] warrant further careful evaluation of the merits of rapid blood replacement and early surgical operation in this condition. Accordingly, since January 1947 we have been testing the value of immediate large blood transfusions and gastric resection in the therapy of grossly bleeding peptic ulcer, and though the work is still in progress it is justifiable to report on methods used, clinical results to date, and tentative conclusions. At present the series comprises 54 patients, 33 of whom were operated upon, and 21 of whom were treated as control cases without operation.

A definition of terms and explanation of criteria used in the selection of cases is in order. By early operation we mean subtotal gastric resection within 24 hours of admission to the hospital. By acute hemorrhage is meant vomiting of blood or passage of blood by rectum with attendant signs of cerebral anoxia within one week of admission to the hospital. To be classified as massive the hemorrhage must have been severe enough to depress the admission red cell count to 2.5 million per cmm or less, or to reduce the circulating red cell volume to 60 per cent of normal or less. Our criteria in the selection of cases in which early operation is recommended may be tabulated, therefore, as follows:

1. The patient must have bled grossly into the upper gastro-intestinal tract within one week.
2. The admission red cell count must be 2.5 mill/cmm or less, or the circulating red cell volume must be 60 per cent of normal or less.
3. There must be reasonably good evidence for the diagnosis of peptic ulcer.

In addition, at least three liters of properly matched blood must be immedi-

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ately available. Operation is advised and carried out at once when these circumstances are present. If the bleeding has been less severe, or conditions are otherwise than as outlined, a non-surgical regimen is instituted and tests are repeated 24 hours later, or with the appearance of further signs of hemorrhage. If the patient or his referring physician show reluctance toward recommended operation, the patient is put into the control series and is treated otherwise as nearly similarly as possible. Blood is given freely and food is allowed as tolerated. Grave associated disease has not constituted a contraindication to operation in this series of cases, but rather the contrary. It seems reasonable that the rapid relief of anoxia and surgical control of hemorrhage would increase rather than impair the patient's ability to survive previously existing disease. Consequently, we have operated upon patients with advanced bilateral tuberculosis, hypertensive cardiovascular disease, extreme obesity, coronary sclerosis, pulmonary emphysema, chronic sepsis and cerebral hemorrhage. If the patient shows signs of hemorrhagic shock, the rate of administration of blood and preparation for operating are speeded up. In several instances operation was started within two hours of admission, while the patient was still hypotensive, but blood was being transfused rapidly at the same time.

Within one-half hour after admission to the hospital blood studies are made by a trained laboratory team, and blood transfusion is started immediately after samples are taken. The measurements include red cell count, hemoglobin and hematocrit, plasma volume, extracellular fluid volume, plasma protein concentration and non-protein nitrogen, plasma chloride and CO_2-combining power, and blood sugar. The analytical methods used are standard methods with which the laboratory staff has had considerable experience[12]. The blood smear is studied for type of anemia and abnormal elements, and the clotting mechanism is investigated to exclude the presence of hemorrhagic diathesis. All blood given the patient is weighed and its hemoglobin and protein content are determined beforehand. Blood loss at operation is measured and in 29 gastric resections in this series averaged 365 cc. Urine volume is measured daily and its content of cells and albumin and its specific gravity and pH are determined. In no instance was the lower nephron syndrome encountered. In patients operated upon liver biopsy is done as soon as the peritoneal cavity is opened, and the glycogen content of the specimen is measured. The blood studies are repeated within 24 hours after the operation, and again before discharge from the hospital.

The program of treatment may be briefly outlined as follows: If the criteria described are fulfilled, operation is advised within one hour after admission to the hospital, regardless of any associated disease, unless the patient is moribund from some cause other than hemorrhage from peptic ulcer. The anesthesia has been ether-oxygen mixture by endotracheal tube at the hands of a senior staff physician anesthetist. Blood is given through two cannulas before and during operation, and to a less extent afterwards.

The average interval between admission and operation has been 9.2 hours, most of which delay is occasioned in obtaining the necessary amount and type of blood.

At operation subtotal gastric resection is done with antecolic Hoffmeister anastomosis, an average of 80 per cent of the stomach being removed as shown by actual measurements. If it is a posterior wall duodenal ulcer, where feasible the ulcer is dissected out. In some instances the procedure described by Allen is employed[4]. In two cases the posterior wall duodenal ulcer had so large a crater and was surrounded by so much acute inflammatory reaction that pyloric transection was deemed advisable. An interesting problem confronts the surgeon when at operation no lesion of stomach or duodenum can be detected and no cause for hemorrhage can be made out after careful abdominal exploration. In this situation extensive gastric resection is performed without hesitation. In 5 such instances the resected specimen has shown shallow ulcers with open vessels, the stomach being involved in 4 cases and the duodenum in one.

TABLE I

	R.B.C. Mill/cmm	Vc %	Circ. Vol. R.B.C. % Norm.	Plasma Protein Gm/100cc	Plasma Volume % Norm.	Serum N.P.N. Mg/100cc
Operated on	2.5	26	48	6.0	100	53
Not operated on	2.9	29	55	5.9	97	43

Average Values for Admission Laboratory Data in Patients with Acute Massive Hemorrhage from Peptic Ulcer (Early Operation in 32, No Operation in 21)

An important technical point in some cases is evacuation of the stomach by gastrotomy before proceeding with gastric resection. The stomach is sometimes distended by a jelly-like cast of blood, and if the clot is carefully milked out through the transected lower stomach extensive gastric resection then becomes feasible.

Following operation penicillin and oxygen therapy are provided, and in the later cases streptomycin. The patient is out of bed within 24 hours for early ambulation. Sodium bicarbonate or sodium lactate is given intravenously to maintain alkalinity of the urine. As a rule little blood is given postoperatively. The average period of hospitalization following operation has been 15 days.

Of the 54 patients in the series to date 33 were operated upon early, and 21 were not operated upon, due to disinclination on the part of the patient or the referring physician. Four of the patients operated upon were found to have other causes for bleeding rather than gastroduodenal ulcer. One had esophageal varices, one hiatal hernia and peptic ulcer of the esophagus, one carcinoma of the cardia and one lymphosarcoma of the stomach. In the latter case gastric resection was performed, in the others only exploratory laparotomy. All four patients made uneventful convalescence.

With regard to diagnosis, reliance has been placed chiefly on the history and physical findings. The passage of stools containing fresh or tarry

blood had been noted by 44 of 50 patients, while 37 had vomited blood. All had either melena or hematemesis. The majority of the patients gave a history of ulcer dyspepsia, though in seven cases the symptoms were of less than six weeks' duration. In 16 patients a diagnosis of peptic ulcer had previously been made by roentgen studies. The most important physical findings were pallor, peripheral evidence of shock, and epigastric tenderness. Blood in the stool and in the gastric contents was also important. Of the entire group of 54 patients 24 showed signs of hemorrhagic shock on admission. Of these 24 patients 15 were in the operative group and the opera-

TABLE II

	Number	Age Average	Age High	Age Low	Blood given, cc Average	Blood given, cc High	Blood given, cc Low
Operated on early	33	54.6	74	22	3,600	9,400	1,000
Not operated on	21	61.0	82	35	2,040	11,000	0

Age and Amount of Blood Given in Patients Operated Upon Early and in Patients Treated Non-Surgically for Acute Massive Hemorrhage from Peptic Ulcer

tion was not postponed but resuscitation and operation were carried out concurrently. The roentgen ray has not been used as a diagnostic aid in this series of cases, as in our judgment the findings of examination under these difficult circumstances are not definitive enough to warrant delay and further manipulation.

Pathologically the bleeding ulcers of this series have fallen into two groups. More numerous have been the deep large indurated ulcers of stomach or duodenum, and often these lesions have penetrated neighboring structures. Less common have been the single or multiple shallow ulcers of stomach, or less often of duodenum, with little or no external or serosal evidence to suggest their presence. These lesions are usually associated with

TABLE III

	R.B.C. Mill/cmm	Blood Volume % Norm.	Total Cir. Hb. % Norm.	Plasma Protein Gm/100cc	Plasma Volume % Norm.	Total Cir. P.P. % Norm	Serum N.P.N. Mg/100cc
Admission	2.5	78	40.0	6.0	100	86	53
24 hours	3.8	95	68.7	6.2	110	99	41
Discharge	4.0	95	70.8	6.6	104	100	28

Average Values for Laboratory Data in 32 Patients Operated Upon Early for Acute Massive Hemorrhage from Peptic Ulcer

a short history. Hemorrhage may be fatal from these rather trivial looking lesions. The single marginal ulcer in the series to date followed gastroenterostomy done many years previously, and gastric resection had to be supplemented by resection of jejunum and transverse colon and cecostomy. Convalescence was satisfactory despite the extent of the operative procedure.

In Table I are shown admission laboratory data obtained prior to treatment in 32 patients operated upon, as compared with 21 not operated upon, average values being shown. The severity of the anemia is obvious. In appraising this factor one must always consider volume as well as concentra-

tion. The reaction to severe hemorrhage consists of shrinkage of circulating blood volume as well as anemia, hence these two laboratory findings must be taken together in setting up criteria for operation and for later assessment of the patient's condition. Plasma protein and plasma volume are far less critical factors in the survival of the patient than total circulating hemoglobin, and in both groups of patients plasma volume was normal on admission. The group treated by early operation are shown to have been more depleted than the group of patients in the control series, particularly with respect to hemoglobin values. The higher non-protein nitrogen figures probably indicate greater blood loss in the group operated upon.

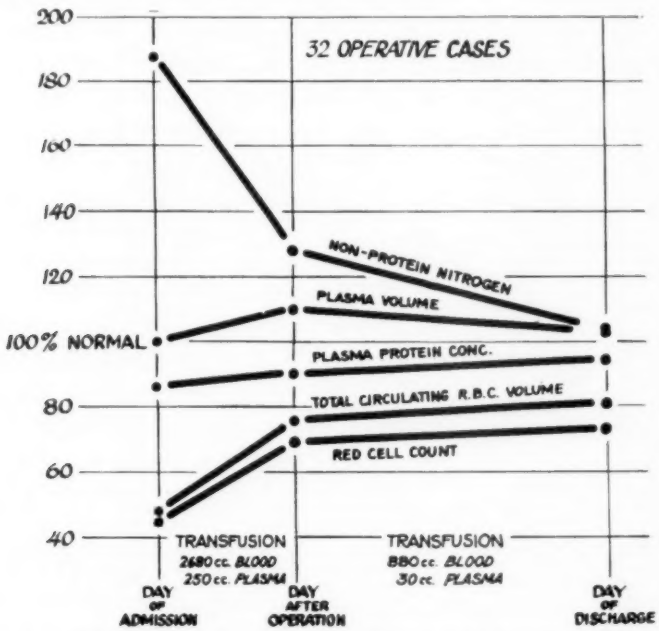

CHART I.—Study of effects of transfusion therapy on total circulating plasma protein and total circulating hemoglobin in ten cases.

In Table II appear data on age and blood transfusion therapy in the two groups of cases. Both groups of patients fell into the older age brackets, in which mortality rate is higher. It happened that the average age of the control group was somewhat greater than that of the group treated by early gastric resection. The patients operated upon received an average of 3600 cc. blood, as compared with 2040 cc. for the control group. In the control group one patient received no blood, as he died of hemorrhage within one-half hour after admission. Conditions were not strictly comparable, therefore, in the two groups of cases, though reasonably similar circumstances prevailed except for the factor of surgical operation. The patient in the non-operative group who received 11,000 cc. of blood eventually succumbed to hemorrhage.

In Table III are shown laboratory data before and after treatment in the group of patients operated upon. It is notable that total circulating hemoglobin values remained at less than 75 per cent of normal despite the administration of 3600 cc. blood, average values being considered. This raises the question of the physiologic nature of the adjustments to hemorrhage and of the subsequent reaction to replacement therapy. In Chart I are indicated further computations bearing on this subject. In 10 patients treated by early gastric resection an effort was made to determine how much of the administered hemoglobin and plasma protein remained in circulation. In all cases the hemorrhage was completely controlled by operation, and there was no reason to believe further bleeding occurred. Processing losses and losses of blood at operation were included in the computations. It is evident that the total circulating plasma protein quickly returned to normal and remained there, despite the administration of 20 to 25 per cent in excess of that theoretically required to achieve normal values. Presumably such excess plasma protein becomes a part of the "metabolic pool," as pointed out by Whipple[13] and Allen, Bogardus, Egner, and Phemister[14], and is subject to the demands of nitrogen metabolism. With respect to the fate of hemoglobin administered in theoretical surplus, the explanation is more difficult. At the end of 24 hours 22 per cent of the administered hemoglobin has apparently left the circulation, while at the end of 15 days 35 per cent is "missing," even though a serious anemia is present. There was no evidence of hemolysis in these cases as a possible explanation for the discrepancy. It is conceivable that the body reservoirs of hemoglobin, called upon in life-endangering hemorrhage, demand repayment of the loan as soon as physiologic stress is relieved. Further investigation of this question is in order. Whatever the explanation for this finding, its practical significance is that much larger amounts of blood are required in the replenishment therapy of hemorrhage than is usually realized. Unquestionably these patients have been given too little blood in the past, whether operated upon or not. Incidentally, we have seen no evidence of over-transfusion in any patient studied. Despite the frequent presence of hypertensive arteriosclerotic heart

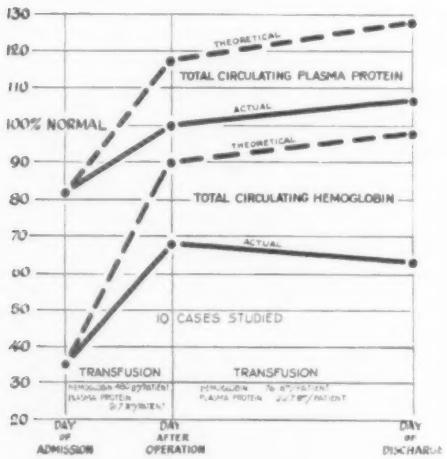

CHART II.—Average values for laboratory data in 32 operative cases of massively bleeding peptic ulcer.

disease in these patients, in none have we seen pulmonary edema, as described by Eaton in animal experiments[15], or congestive failure.

In Chart II are shown in graphic form average values for plasma protein concentration, plasma volume, red cell count and total circulating red cell volume before and after treatment in 32 patients operated upon. The average interval between points 2 and 3 was 15 days. The rapid decline of the initially elevated serum non-protein nitrogen to normal is worthy of note.

Table IV contains data bearing on carbohydrate metabolism. Elevation of blood sugar was found to be the rule in the hemorrhagic state, and the

TABLE IV

Blood Sugar Mg/100cc			Hepatic Glycogen Gm/100Gm		
Average	High	Low	Average	High	Low
164	300	112	2.9	6.2	0.3

Blood Sugar and Hepatic Glycogen Values (Liver Biopsy) in 16 Patients Operated on Early for Acute Massive Hemorrhage from Peptic Ulcer

TABLE V

	Number	Deaths
Patients treated surgically.....	33	5 (15%)
Gastric ulcer	12	3
Duodenal ulcer	16	2
Marginal ulcer	1	0
Other lesions	4	0
Patients not operated on.....	21	6 (29%)

Results from Early Operative and Non-Surgical Management of Acute Hemorrhage from Peptic Ulcer

average value of 164 mg. per 100 cc. is to be compared with the normal of 80 to 120 mg. per 100 cc. for the method used. In 16 cases just after the peritoneal cavity was opened the liver was biopsied and the glycogen content of the sample was measured. Definite reduction in hepatic glycogen was the rule. Presumably both these findings are related to activity of the sympathico-adrenal system, and possibly also to preceeding deficiency in caloric intake. The evidence indicates the need for the early administration of an adequate caloric supply to these patients.

In Table V the mortality rates in the two groups of cases are indicated. The series is hardly large enough to warrant statistical analysis, but those of us concerned with the work believe that more lives are being saved by the program of early adequate blood replacement and gastric resection than by the non-surgical plan of treatment. The surgical resident staff, on whose shoulders falls the major part of the work of this rather gruelling program, are among its most enthusiastic proponents. If the resident staff is truly convinced of the value of a method—as all chiefs of teaching clinics know—the method must have real merit.

In conclusion, evidence has been presented which tends to favor early restoration of hemoglobin values and gastric resection as the method of

choice in the management of acute massive hemorrhage from peptic ulcer. The advantages of the method as seen at present are:

1. Hemorrhage is controlled directly
2. Mortality rate is lowered
3. Definitive treatment is provided for the peptic ulcer diathesis
4. Early resuscitation and relief of anoxia is achieved
5. Diagnosis is established in doubtful cases
6. Pyloric obstruction when present is relieved
7. Less blood is required in many cases

The method is not to be recommended, however, unless adequate facilities are at hand, and these may be summarized as:

1. Expert 24-hour laboratory service
2. Adequate blood bank
3. Skillful anesthesiologic service.
4. Expert surgical judgment and technique
5. Expert resident and nursing care

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DR. ALLEN O. WHIPPLE, New York: I do not know of anything more trying or more difficult than to be called in consultation on a patient who has been bleeding for days, and finally the medical group call in the surgeon to advise further therapy. Many

of these patients are in a marked state of depletion, they are the worst kind of surgical risks, and when the surgeon advises surgery he is faced with a very difficult problem. Furthermore, many times exploration has been done in an attempt to find the bleeding point or stop the bleeding, and because of the condition of the patient attempts to resect them have not been made. That type of surgery is not very effective. It seems to me that when this type of case is seen early and there has been severe bleeding, the indication for extensive transfusion is very definite, and in that respect indications differ from those where extensive operations are done but the patients are over-transfused. I am sure that many patients at present are being over-transfused in operations where they have not lost a great deal of blood, but where transfusion has been given on the theory of prevention of shock. I am sure, as Dr. Stewart has said, that this question should be very thoroughly investigated. In fact, I heard a short time ago of a patient who had to have a phlebotomy because he had been given too much blood.

In regard to patients with the type of ulcer most conducive to severe hemorrhage, that is, the ulcer situated in the lateral mesial aspect of the duodenum, where resection of the stomach will not necessarily control the bleeding, there is one point that seems to me worth considering; that is, to identify the gastroduodenal artery and ligate it. Of course the inferior pancreatico-duodenal may continue to be a source of hemorrhage, but I think the majority of cases bleed from the superior pancreato-duodenal artery, and for that reason ligation of the main arteries entering the ulcer is an added safeguard.

This series that Dr. Stewart has reported seems to me to be very timely, and emphasizes the importance of not delaying surgery too long in the care of the severely bleeding gastric or duodenal ulcer.

Dr. Edward D. Churchill, Boston: Dr. Stuart has introduced a fundamental problem of hemorrhage. As surgeons, we have been concerned with the immediate effects of acute massive hemorrhage; in other words, the effects on the intravascular blood volume, and have focussed our effort on the development of resuscitative measures to control shock. Once the patient had recovered from the acute crisis, however, it was felt that the job was finished. If the patient had a residual hypochromic anemia, it was thought time and iron therapy were sufficient. I am quite certain that this is the point of view now held by many internists with regard to hemorrhage from ulcer. If the patient survives the immediate crisis of hemorrhage, then the residual hypochromic anemia is a simple medical problem. The real tragedy comes when a second emergency arises before complete compensation is established. This is an event peculiar to bleeding ulcer and not infrequent. I have heard it pointed out repeatedly by Dr. Allen that such a patient cannot tolerate the crises of further hemorrhage and surgical operation. This is a very sound observation, and Dr. Stewart is posing the question of why it is true.

The data presented on the disappearance of hemoglobin (54 hours after replacement therapy, 22 per cent hemoglobin missing; and after fifteen days, 35 per cent hemoglobin missing) raise important problems. Dr. Stewart suggests tentatively that the body is recalling the hemoglobin for its stores. He finds no evidence of hemolysis. It is useless to speculate, but the hypothesis should also be entertained that the body may be calling on the red cells for something other than hemoglobin. Dr. Stewart himself, a number of years ago, showed the diuresis of potassium that occurs after massive hemorrhage. In the face of generalized depletion in intracellular electrolytes, possibly the body calls for any excess balance of these items carried by the red cells.

A similar situation was encountered in the management of battle casualties. There was acute massive hemorrhage associated with the wounding, massive blood replacement—more blood than was lost, perhaps—to get the patient through the crucial initial

surgery, and yet two or three days later when the wounded man arrived at a general hospital, a profound anemia existed. These observations of Dr. Stewart link in with other studies that are being carried on. Those of Dr. Lyons and Dr. Gage were reported last year from New Orleans. I am certain that in the next few years the surgeon will extend his concern about the management of hemorrhage to the late effects of acute blood loss on the body tissues as a whole.

Dr. William C. White, New York: I thought it would be interest to emphasize a couple of points in which we have become greatly interested at Roosevelt Hospital in New York. About a year and a half ago we had the problem of treating a case of massive hemorrhage that had been admitted to the medical service and kept there for ten days. He had been given 8000 cc of citrated blood. One of my associates operated on this case, was thoroughly satisfied with the procedure, but at autopsy three days later we found there had been no evidence whatsoever of repair of the tissues, although he felt that he had performed a meticulous excision of ulcer with pyloroplasty. We believed that the long wait plus the introduction of so much foreign blood had done something to the reparative power. For that reason, we have decided to operate within 24-36 hours or not at all, during the acute phase. We have become satisfied with this policy. For that reason, in agreement with the medical service, we have made it a practice to admit all massive hemorrhage cases to the surgical side.

We are in complete accord with what Dr. Stewart has said, but I would like to emphasize a factor which he perhaps did not have time to mention. We routinely use a thin barium by mouth in all these cases, even though they are extremely sick. We do not allow fluoroscopic pressure, as we are a little fearful of what might happen. If we cannot get any evidence of ulceration of the stomach or duodenum, we treat these cases in a palliative fashion.

Dr. J. E. Rhoads, Philadelphia: I think we are all in agreement with the principle that many of these patients should be operated upon earlier than has been the case in the past, and that we should avoid having them carried along for many days in medical wards and then turned over for surgery practically in extremis. However, I wonder somewhat whether it is necessary to divide all this group of patients at once into those we are going to operate on immediately and those whom we are not going to operate on at all. It seems to me there is a good deal of experience to show that large numbers of these patients will stop bleeding spontaneously, and that they can be operated upon more safely after they have recovered from the immediate effects of hemorrhage. For that reason, many of us have felt it better to give most of them a chance to stop bleeding on a medical regimen. Admittedly, this increases the risk somewhat for those who will not stop bleeding, but after all, this group is in the minority. It should make the overall mortality lower because those who do stop bleeding will recover from the effects of the hemorrhage and can then be operated on in the interval, while those who do not stop bleeding can still be operated on after a trial period on a Meulengracht regime, with success in a large percentage of cases.

Dr. Gavin Miller, Montreal: Massive hemorrhage in the older group gives a high mortality and multiple transfusions may tide these patients over the crisis but, as Dr. Churchill pointed out, they do not respond as well to further transfusions if a second crisis occurs, no matter how much blood is given. I am inclined to consider transfusions as a temporary assistance, but not to consider that a transfusion in all ways take the place of the blood lost. It is a foreign body, and given in too large quantities may overstep the margin of safety and cause damage. When skin grafts are used from parent to child as a temporary means of covering burned areas they "take" but do not live, and gradually disintegrate. I think that blood probably acts in a similar way when given to another person, and soon is destroyed. This is perhaps the reason for the marked secondary anemia which may be difficult to overcome after

prolonged hemorrhage. For 20 years I have advocated "immediate" operation; that is, if bleeding does not stop within 24 hours, on patients past 45 years of age who are admitted with massive hemorrhage. In this group of patients—who number 8 or 9—no fatality has occurred when the stomach was resected. Had those patients been allowed to bleed on for days, a higher mortality would have occurred, as all statistics on bleeding ulcer tend to show.

DR. CHARLES G. JOHNSTON, Detroit: Dr. Stewart's presentation seems to me to be a very timely one. We have treated these patients in the past expectantly, and all too often there is great difficulty in having surgeons see these patients early enough to follow them well or to treat them. In many institutions it is common practice for bleeding peptic ulcers to be admitted to the medical ward, and for the internist to call the surgeon only when he has failed completely, and in many instances the surgeon is called when the patient is practically moribund. Recently, with some difficulty, we have been able to have these patients admitted directly to surgery, and our experience with them has been much better. We have found, as I am sure most of you have, that an operation in the early stages with adequate replacement of blood at the time of operation, is a lot less likely to cause death than a similar operation two, three or four days later, after the patient has been bled out several times and has had frequent blood replacement. Dr. Stewart's discussion of this is very interesting to me.

When such a patient is admitted to our hospital he goes to the surgical ward. If he is bleeding from the upper gastro-intestinal tract a stomach tube is passed into the stomach, and the stomach is well washed out. One of my associates, Dr. Byrne Daly, has amply demonstrated that it is quite possible to keep the stomach alkaline enough by the administration of phosphate buffers to permit the action of thrombin. The stomach is washed out, the phosphate buffer is introduced, the tube is kept in place with light suction and then 10,000 units of thrombin is added. If the thrombin is going to work, it works very soon, and within an hour or two one can tell whether the patient is going to stop bleeding. If he continues to bleed we recommend, regardless of his age, that he be operated upon and usually a gastrectomy is performed. We have felt this to be much more in keeping with sound principles of surgery. If a patient were bleeding externally, a direct attempt would be made to stop it. It seems to me that it is quite difficult to tell what is happening or is going to happen to the patient if one does not know and cannot determine the amount of bleeding. We find it quite necessary to continue alkalinization with the buffer solution for a fair period of time after bleeding stops. In the first cases we were not successful because, after the bleeding stopped, we stopped giving the buffer solution. We interpreted our failure as due to digestion of the soft clot which had been formed. It is quite obvious that thrombin will not stop bleeding in an open vessel of any size, but many patients bleed through smaller vessels and without a great deal of force, and many of them do stop after thrombin and buffer is given. Those that continue to bleed should receive early surgical treatment.

DR. JOHN D. STEWART, Buffalo (closing): I think you must have noted that, in the discussion, the time factor has been mentioned repeatedly. It seems to me that this is one of the crucial aspects of this question. A patient with massive bleeding from an ulcer of the upper gastro-intestinal tract is to be considered a surgical emergency. Certainly such patients should be admitted on the surgical rather than the medical service. The time factor is of utmost importance.

It used to be stated by the older surgeons, who based this on accumulated sound observation, that a patient who was bleeding massively from an ulcer would respond to one transfusion, possibly even two, but not to the third. That has been an interesting consideration to me. There are at least two explanations that come to mind. In the first place, undoubtedly one, two or three pints of blood under the circumstances

was inadequate replacement; but the second point, more interesting, is that during the course of massive hemorrhage and shifts of body fluids, a great many metabolic changes undoubtedly take place which have not been fully understood. It is not inconceivable that the enzymatic functions of the liver may be seriously disturbed by sublethal anoxia and precipitate irreversible changes. There is need therefore for early decision as to definitive treatment in these cases and that is one of the main points I want to bring out. In the selection of cases for early operative treatment various criteria have been advocated from time to time. I am doubtful of the value of such a policy for I do not believe it is possible to tell with any degree of assurance which patients will stop bleeding. I am particularly opposed to a "wait and see" policy, for during the period of procrastination irreversible changes in vital organs may occur and the opportunity to perform effective surgery may be lost. With respect to the age factor, statistically speaking older patients are unquestionably less tolerant of massive hemorrhage. However, some young patients die and some old patients survive. Our approach to date has been more in the direction of setting up an active plan of treatment which offers the best prognosis regardless of age.

THE SURGICAL TREATMENT AND THE PHYSIOPATHOLOGY OF COARCTATION OF THE AORTA*†

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Coarctation of the aorta belongs to the group of congenital cardiovascular malformations in which arteriovenous shunts are absent, and in which there is no cyanosis. Fortunately, diagnosis is not difficult in most cases if one recalls that there is usually hypertension in the upper part of the body and hypotension below. There is usually evidence of increased collateral arterial pathways in the upper part of the body, absence or suppression of arterial pulsations in the lower extremities, and notching of the ribs in the older patients. A systolic murmur may be present. The stenosis or atresia can usually be visualized by angiocardiography. The complications associated with severe coarctation include those accompanying hypertension due to other causes.

This paper consists of a consideration of the surgical treatment and the physiopathology of coarctation of the aorta. The surgical treatment will be considered first.

The first method for treating coarctation was published by Blalock and Park[1] in March, 1944, in a paper entitled "The Surgical Treatment of Experimental Coarctation (Atresia) of the Aorta." In brief, this method consisted of using the left subclavian artery as a pathway by which the blood could be shunted beyond the point of stenosis. The use of this method was not attempted on patients at this time, and in the latter part of 1945 Crafoord and Nylin[2] and Gross and Hufnagel[3] reported a better method. This consisted of excision of the stenotic area and the performance of an end-to-end anastomosis between the proximal and distal ends of the aorta. The first operation on a patient by Crafoord was on October 19, 1944, and that by Gross on June 28, 1945. Clagett[4] of the Mayo Clinic was the first to use the subclavian artery to by-pass the point of stenosis in patients.

Everyone is agreed that the ideal operation is one in which the stenotic area is excised and the proximal and distal ends of the aorta are united by suture. Unfortunately there are some instances in which this does not appear to be feasible. Most frequent among these are those cases in which the atretic area is long and those in which the aorta is so diseased that end-to-end suture following excision is not feasible. The question has been raised as to whether one should employ the left subclavian to by-pass the point of stenosis if the ideal operation cannot be performed. It is our contention that this method

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should be used providing one does not have to sacrifice the large intercostal collateral arteries which arise from the aorta just beyond the point of stenosis. It is usually possible to save these blood vessels. It is our impression that the transposed subclavian artery will convey more blood to the lower part of the body than will the collateral vessels from the undivided subclavian artery.

There are several points about the technic of the operation which are worthy of brief comment. The first of these is concerned with the incision. In some of the earlier operations the posterior half of the fifth rib was removed and the paravertebral ends of the fourth and sixth ribs were divided. We now follow the recommendation of Crafoord in removing practically the entire length of a rib, usually the fifth, and it is not necessary to divide other ribs. An adequate exposure is obtained and there appears to be less discomfort and dyspnea in the postoperative period. Furthermore, there is less damage to intercostal blood vessels.

In the earlier operations which we performed, one or more pairs of intercostal arteries immediately distal to the point of coarctation were doubly ligated and divided. With additional experience we now follow the advice of Crafoord in trying to spare these arteries. In the first place these vessels are very large and thin walled, and one may encounter troublesome bleeding as a result of attempted ligation and division. In the second place these arteries are important collateral pathways, and it is particularly important to preserve them in case difficulty should be encountered in completing the anastomosis. The intercostals just distal to the coarctation may be occluded with one or more rubber-shod clamps. Fortunately, these vessels run upwards and do not interfere with approximation of the ends of the aorta while the anastomosis is being performed.

In the majority of patients with coarctation of the aorta the point of stenosis is only a short distance beyond the point of origin of the left subclavian artery. Obviously one can occlude the left subclavian artery as well as the aorta during the time required for excision of the stenotic area and the performance of an end-to-end anastomosis, but this decreases the quantity of blood which reaches the lower part of the body during this procedure. We have been able to escape this added danger by using a modified Potts arterial clamp which occludes the aorta completely, but permits some circulation through the subclavian artery. This clamp is introduced in the free space between the points of origin of the left common carotid and the left subclavian arteries. It is shown in place in Figure 1.

A single layer of sutures which includes the entire thickness of the wall of the aorta has been used in our operations and in those by Gross. This point is mentioned because Crafoord has attempted to avoid inclusion of the intima of arteries in his anastomoses. It is our opinion that one obtains a smoother intimal surface and a stronger arterial wall with less tendency to the formation of aneurysms when the entire thickness of the wall of the vessel is included in the suture.

It is probably a matter of personal choice as to whether one employs an everting or an overhand suture in performing the anastomosis. We prefer the former type because it leaves less suture material and smoother intimal surfaces in contact with the flowing stream of blood. The suture material which we use is 0000 silk on small round needles (Deknatel).

Following the completion of the anastomosis, we have followed the advice of Gross in releasing the occlusion of the aorta slowly and at the same time lowering the patient's head and introducing blood intravenously rather rapidly. In one patient the heart's action became slow and feeble but it improved on reapplication of the clamp. Subsequent removal of the clamp was tolerated without incident.

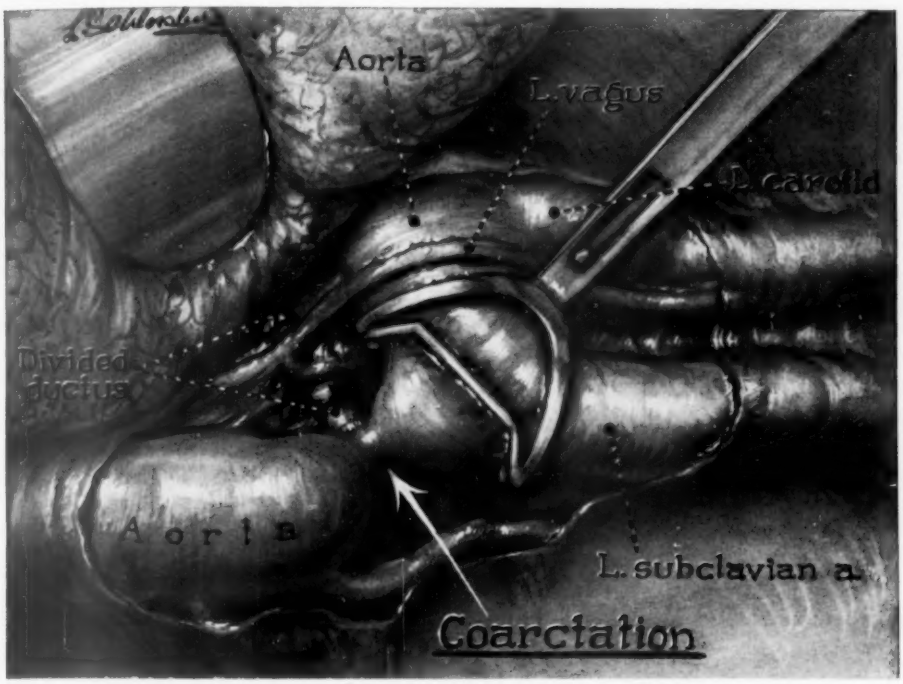

FIG. 1.—Illustrates the modified Potts clamp in position. It may be seen that while it occludes the aorta completely, it permits blood to flow through the subclavian artery.

Our operative experience is limited to 23 patients with coarctation of the thoracic aorta. The ages varied from 7 to 31 years. Thirteen of the patients were 20 or more years of age. An anastomosis was attempted in 22 of the 23 cases and was completed in 21 of them. In the one case in which the anastomosis was not attempted the site of coarctation was several interspaces below the usual site and the constriction was longer than usual. Furthermore, the distal aorta was somewhat hypoplastic and was surrounded by adhesions. In the case in which the anastomosis was attempted but not completed, the proximal aortic clamp became dislodged, resulting in sudden stoppage

of the heart after approximately one pint of blood had been lost. Even though control of the vessel was obtained quickly, efforts at resuscitation failed. As a result of this experience, a mechanism for locking the aortic clamps was devised.

An anastomosis was completed in 21 of the 23 cases. In 17 of these the site of coarctation was excised and an end-to-end anastomosis was performed between the proximal and distal ends of the aorta. The only fatality in this group was a 13-year-old boy in whom a cerebral thrombosis of the left internal

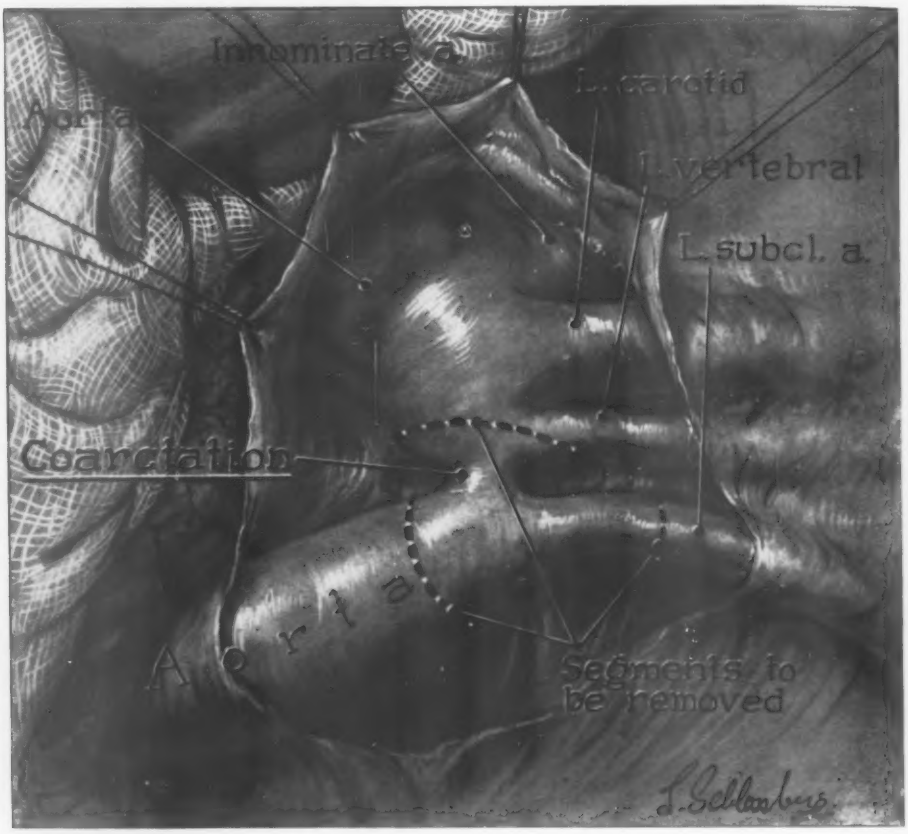

FIG. 2.—Reveals the findings in a patient in whom the subclavian artery arose distal to the point of stenosis.

carotid and left middle cerebral arteries occurred postoperatively. It was noted preoperatively that he stuttered quite badly. The operative procedure was an easy one and no difficulty was encountered. The only other complication in this group was the development of a sixth cranial nerve paralysis on the right in a recent patient. It was felt that this may have been caused by a pre-existing intracranial aneurysm.

In four patients the proximal segment of the aorta was considered to be too short for an end-to-end suture, and the left subclavian artery was used

to by-pass the point of stenosis. Most of these cases occurred in the early part of the series and it is likely that with additional experience an end-to-end anastomosis could have been performed in some of them. There was one death in this group. The patient was a child of seven who had evidence of heart failure with pulmonary hypertension preoperatively. Free pleural fluid and pulmonary edema were present at the time of operation. The anastomosis was performed without difficulty but the child died as the chest was being

FIG. 3.—Shows the completed anastomosis. It may be seen that the subclavian artery has been divided, and that the suture line extends onto the base of the vertebral artery.

closed. Mitral stenosis, thickening of the tricuspid valve, pulmonary arterio- and arteriolar sclerosis, and pulmonary edema were found on postmortem examination. A second patient in this group developed a partial paralysis of the legs as a result of the operation. It was the opinion of the consulting neurologist that this was due to an occlusion of the anterior spinal artery which may have been aberrant.

If we consider the two groups together, it is to be observed that there were three deaths in the 22 cases. Two of these occurred in the younger age group

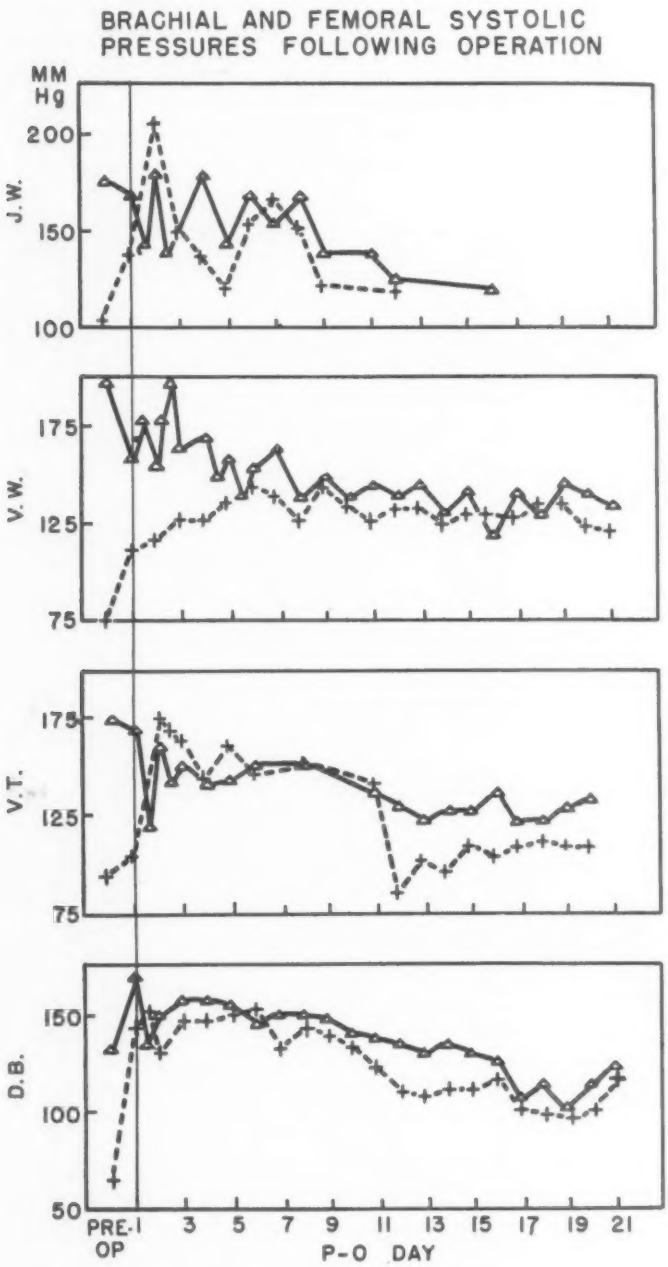

FIG. 4.—Charts the changes in blood pressure following resection of the stenosis. The solid line represents brachial systolic pressures; the broken line femoral systolic pressures.

and one in the older. The latter death was due to a technical error at the time of operation and should have been avoided. Cerebral thrombosis in one case and pulmonary edema in the presence of valvular disease and pulmonary sclerosis in the other accounted for the two deaths in the younger age group.

The findings in one of the cases were of sufficient interest to merit specific comment. Physical examination and angiocardiography in a female of 26 indicated that the coarctation was proximal to the orifice of the left subclavian artery. Arterial pulsations in the left arm were weaker than those in the right, and notching of the ribs was present on the right and not the left. On exploratory thoracotomy it was found that the left subclavian artery arose from the aorta immediately distal to the point of stenosis. Temporary occlusion of this artery did not cause a diminution in the radial pulse on the left; in fact, the anesthetist thought it caused the pulse to become stronger. The flow of blood in the left subclavian artery was the reverse of the normal direction. The orifice of the left subclavian was so close to the site of coarctation that it appeared to be necessary to sacrifice it in doing an excision of the stenotic area and an end-to-end anastomosis. A diagram of the operative procedure is shown in Figures 2 and 3. A satisfactory result has followed this operation.

During the three weeks postoperative period that our patients have remained in the hospital, two observations have been made which seems worthy of comment. In every case where headache has been a prominent preoperative symptom, it has been conspicuously absent postoperatively. It has also been noted that the systolic blood pressure in arm and leg require some five to ten days to stabilize. This is illustrated in Figure 4, and has been commented upon by Gross[5] and Shick.[6] Follow-up studies upon these patients are currently in progress.

Studies on the *physiopathology* of this malformation have dealt primarily with the etiology of hypertension in the upper part of the body. Therefore, most investigators have been concerned with the relationships of blood pressures, blood flows, and vascular resistance in the upper and lower extremities. Conclusions drawn from the studies have been controversial. Blumgart found normal arteriolar pressures in the arms and legs and concluded that the elevation in blood pressure was the result of the resistance offered by the aortic stricture and the collateral pathways.[7] Similar conclusions were reached by Lewis, who found normal blood flow through the arm and leg, but observed vasodilatation in the head, neck, and hand.[8] More recent studies, however, have emphasized the role of peripheral arteriolar resistance. Pickering postulated an increase in arteriolar resistance limited to the upper part of the body and attributable to vascular narrowing.[9] Prinzmetal and Wilson found decreased blood flow through the arm and concluded that arterial hypertonus of vasomotor origin must be present in the upper limbs.[10]

The introduction of intra-arterial blood pressure measurements in man by Hamilton's method opened a new line of approach.[11] Using this technic, Steele

found elevations above normal of the diastolic pressure in the radial and femoral arteries. This was interpreted as evidence of a generalized increase in arteriolar tone throughout the body.[12] According to Rytand, interference with the renal blood supply caused by the stricture of the thoracic aorta was responsible for the increased resistance.[13] This conclusion was supported by the finding of Goldblatt that hypertension occurred if the aorta was constricted

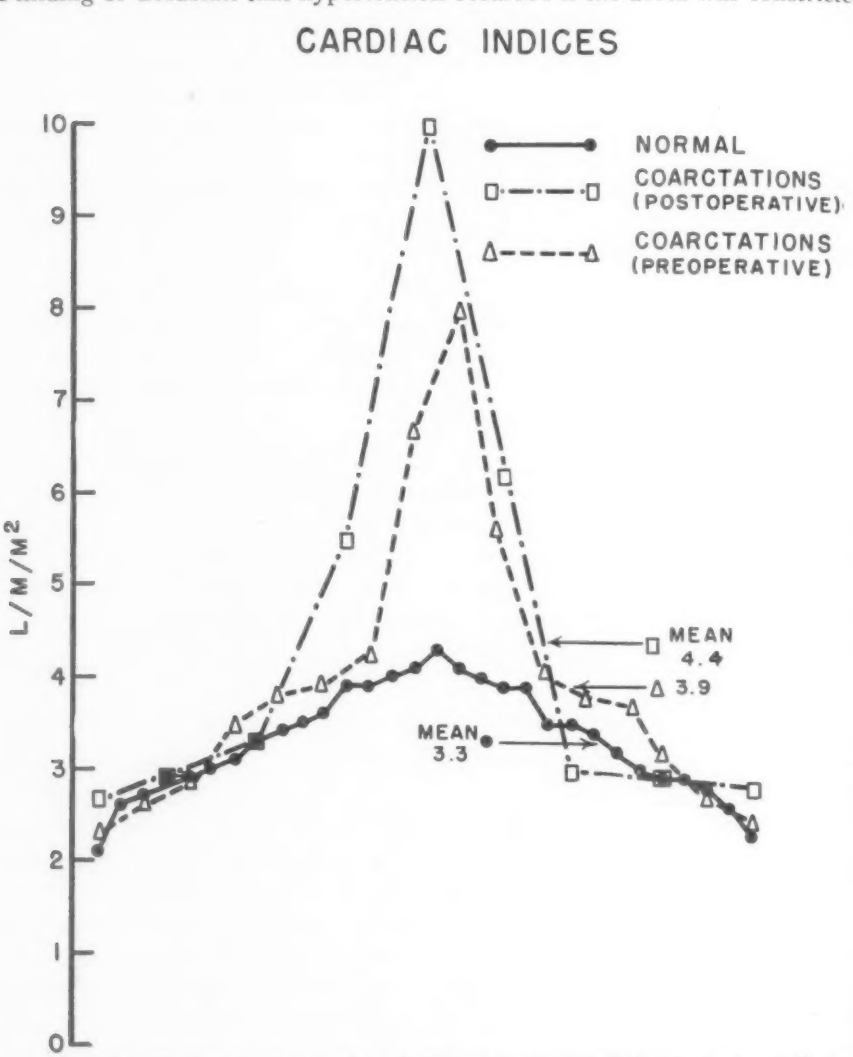

FIG. 5.—Illustrates the cardiac indices of normal individuals as well as patients with coarctation of the aorta both pre and postoperatively. It may be seen that the cardiac indices show no significant deviations from normal values.

above the level of the renal arteries and failed to appear when the aorta was constricted below.[14] Increased renal vascular resistance, observed in cases of coarctation of the aorta, might be construed as further evidence of the participation of the kidney in the production of hypertension.[15] On the other

hand, hypertension in the arm has been observed in several cases of coarctation where the stricture was below the level of the renal arteries. In one of these the renal blood flow was normal.[16]

This short review of the literature illustrates the variety of results and interpretations. The introduction of surgical therapy is of such recent date

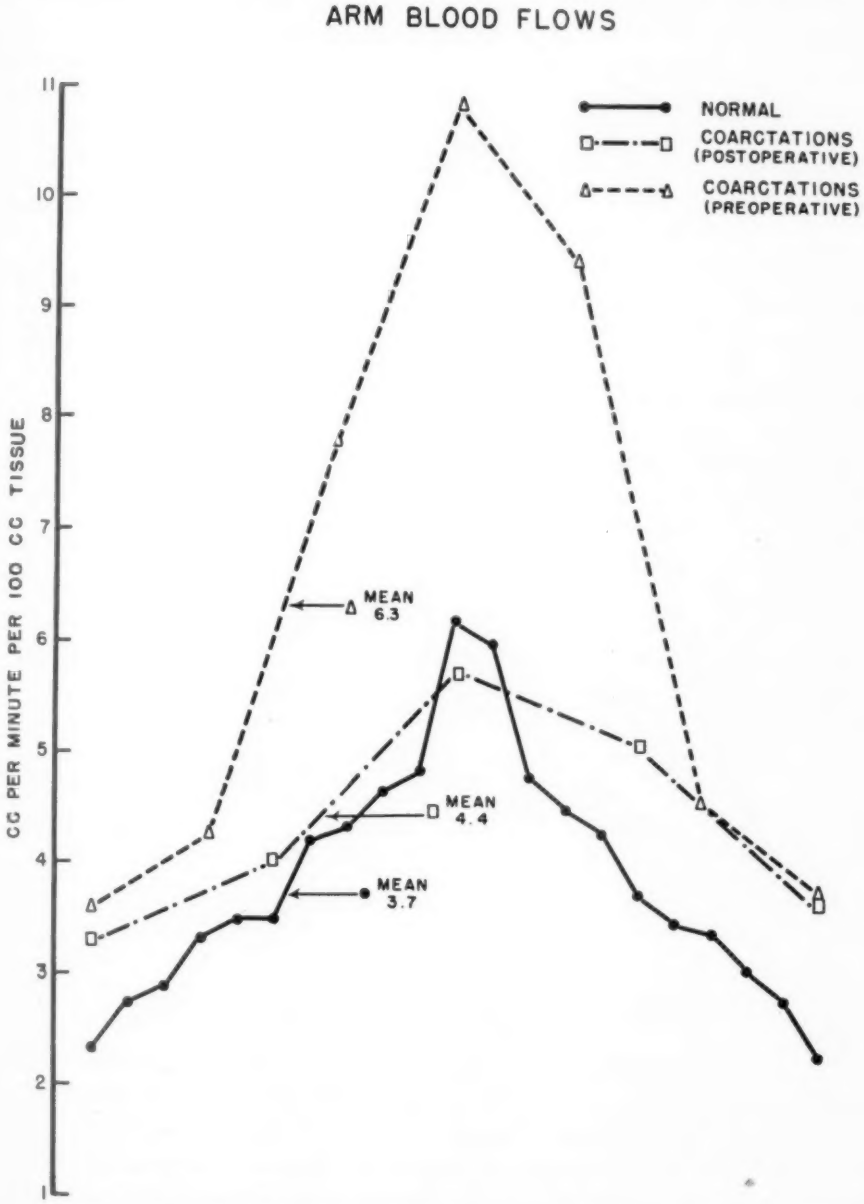

FIG. 6.—Shows that the mean preoperative blood flow through the forearm of patients with coarctation is markedly elevated. Postoperatively it falls to essentially normal levels.

that few reports dealing with postoperative changes have been published. The succeeding paragraphs of this paper deal with studies concerning the pre- and postoperative hemodynamics in coarctation. The mechanisms leading to hypertension will be discussed in the light of these findings.

A total of 22 patients were studied. Postoperative investigations were carried out three weeks following surgery. Cardiac output was determined according to the Fick principles using right heart catheterization for sampling of mixed venous blood.[17] All cardiac outputs were expressed in liters per minute per square meter of body surface (cardiac index). Blood gas analyses

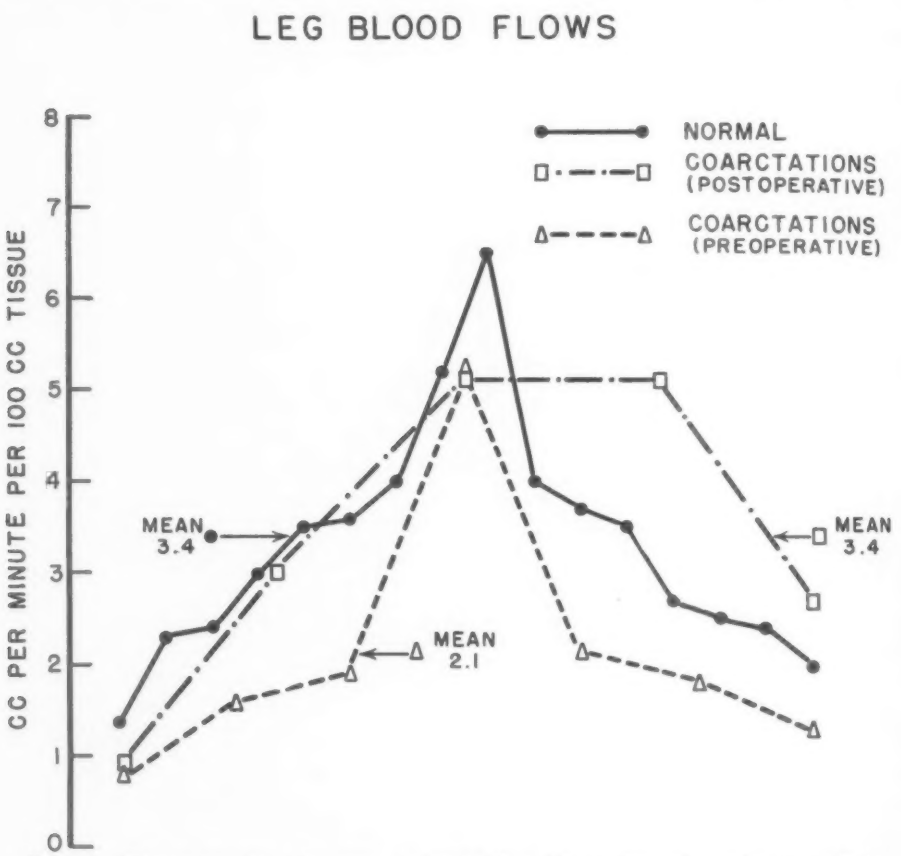

FIG. 7.—Illustrates that the mean preoperative blood flow through the calf is slightly below normal values, rising postoperatively.

were carried out in the manometric apparatus of Van Slyke and Neill.[18] Analyses of respiratory gases were performed using the apparatus of Haldane[19] and the Pauling oxygen analyzer. Intra-arterial blood pressures were determined using hypodermic strain gauge (Statham) or Hamilton manometer.[11] Mean pressures were derived by planimetric integration of the area under the pressure curve. Renal blood flow and glomerular filtration rate were determined in most of these individuals by Dr. Jacques Genest and co-workers using the

clearances of para-amino hippuric acid and sodium thiosulfate. Their studies form the subject of a separate report, but reference will be made to their results. Blood flows through the leg and forearm were measured at 32° C. with the plethysmograph described by Wilkins and Eichna.[20] Their results on 14 normal individuals agreed closely with those obtained on five normal individuals in this laboratory. The combined data were used in the statistical evaluation of normal blood flows through the forearm and leg. There is considerable disagreement in the literature concerning values for normal blood flow through the extremities.[8, 12, 20] This appears to be primarily the result of differences in the apparatus used and of variations in the temperatures at which determinations were made.

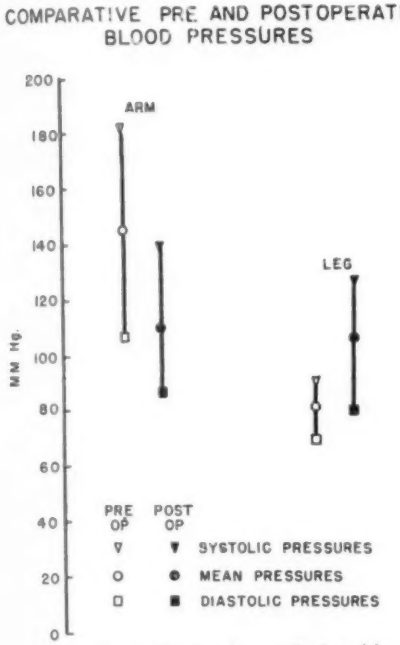

FIG. 8.—Shows the relationship of intraarterial systolic, diastolic, and mean pressure in arm and legs pre and postoperatively. It may be seen that after operation pressures tend to equalize.

Figure 5 illustrates the preoperative cardiac indices of 16 individuals; in nine, the indices were determined postoperatively. It may be seen that there was some scatter of the figures. In three instances the pre- and postoperative values for cardiac outputs were significantly elevated above normal. However, the remainder of the data fell within the normal range established by Cournand and his associates. (Fig. 5.)[21] It may be concluded, therefore, that the cardiac output of patients with coarctation of the aorta before and after resection of the stenosis is within normal limits.

The blood flow through the forearm was determined preoperatively in seven cases. Postoperative observations were made in five individuals. Figures 6 and 11 illustrate that the preoperative blood flows through the arm were significantly elevated above normal, with a mean value of 6.3 cc./min./100 cc. arm tissue, as compared with a normal of 3.7 cc. Postoperatively the blood flow through the forearm decreased toward normal. (Figs. 6 and 11.) In contrast, the preoperative blood flow through the calf, determined in the same individuals, was below the standard deviation of the normal, with a mean of 2.1 cc./min./100 cc. leg tissue as compared to 3.4 cc. in the normal. (Figs. 7 and 11.) Postoperatively the flow through the calf, measured in five cases, rose to normal levels. These findings are at variance with those obtained by

Lewis, who found normal blood flows in both upper and lower extremities.[8] Low flows through the arm and hand were described by Prinzmetal and Wilson.[10] It is probable, however, that the results are not comparable because of the variations in the techniques.

Direct intra-arterial blood pressure determinations from the brachial and femoral arteries were performed in 17 preoperative cases. (Fig. 8.) In seven of these, pressures were recorded simultaneously. (Fig. 9.) Figure 9 shows the elevation of the systolic and mean pressures in the arm.* With two excep-

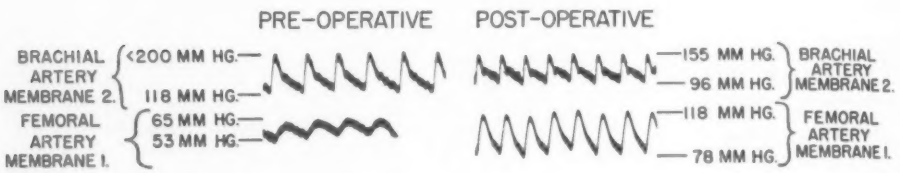

FIG. 9.—Is a simultaneous direct pressure recording from the brachial and femoral arteries before and after operation.

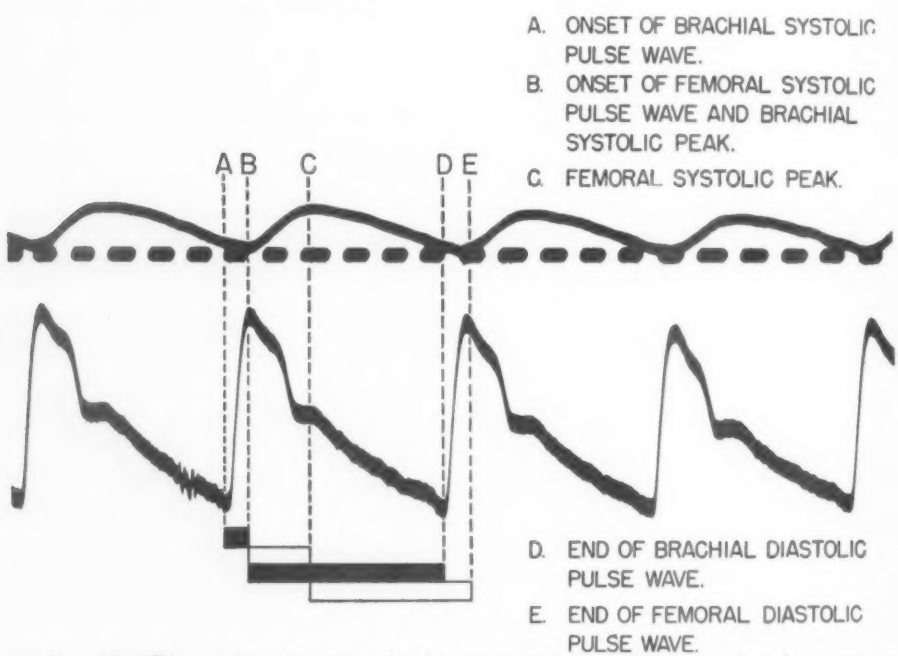
A. ONSET OF BRACHIAL SYSTOLIC PULSE WAVE.
B. ONSET OF FEMORAL SYSTOLIC PULSE WAVE AND BRACHIAL SYSTOLIC PEAK.
C. FEMORAL SYSTOLIC PEAK.
A B C D E
D. END OF BRACHIAL DIASTOLIC PULSE WAVE.
E. END OF FEMORAL DIASTOLIC PULSE WAVE.

FIG. 10.—Shows the alterations in the components of the femoral pulse wave as compared with the brachial pulse wave. The delay in the onset of the femoral upstroke, and the difference in duration of brachial and femoral upstrokes in demonstrated.

* Following the criteria of the American Heart Association, the upper limit of normal systolic pressure was taken as 140, the upper limit of normal diastolic pressure was taken as 90 mm. Hg. The upper limit of normal mean pressure was considered to be 110 mm. Hg.

tions, the diastolic component was also elevated. The pulse pressure was increased. Postoperatively the systolic, diastolic and mean pressures fell in most instances. (Fig. 8, Table I.)

The systolic blood pressures taken from the femoral artery of 15 individuals were below normal in every instance. In only one patient was the diastolic pressure higher than normal. Mean pressures were not elevated. Postoperatively, the systolic and mean pressures rose, the diastolic component remaining almost constant. (Fig. 8.) These findings corroborate those of King, Steele, Gross, and others.[22, 12, 5]

The contours of the femoral and radial pulse waves have been compared by Woodbury and by Brown and their associates.[23, 24] These investigators found the brachial pulse contour of normal appearance. Pressure curves from the

TABLE I.—*Direct Blood Pressure Determinations in Coarctation*

	Preoperative				Postoperative			
	Arm		Leg		Arm		Leg	
Name	S/D mm. Hg	Mean	S/D mm. Hg	Mean	S/D mm. Hg	Mean	S/D mm. Hg	Mean
E. W.	205/122	150	105/89	97				
A. W.	196/107	136	98/80	91	157/77	98	154/92	122
M. O.	133/103	114	115/98	103	112/65	88	147/85	106
B. C.	200/115	162						
W. D.	171/93	135	125/52	91			148/90	110
H. S.	186/118	170	102/78	87			109/72	88
C. S.	150/38	142	88/66	77	160/140	147	89/72	78
D. P.	>200/134	173	78/62	72	120/75	91	125/74	87
W. B.	>200/118	174	65/53	61	155/96	128	118/78	93
C. C.	150/107	132						
B. A.	>200/100	144	52/45	48				
V. W.	200/97	170	68/52	63	124/84	104	109/73	88
J. W.	178/91	144	100/77	92	144/71	96	112/66	88
R. K.	200/92	162	96/73	88	178/98	140	178/102	140
V. T.	175/88	127	97/74	84	134/70	108	142/73	125
A. P.	>200/100	160	91/61	78				
D. B.	134/62	98	66/52	62	122/71	92	108/58	79
Arith. Mean	>183/106	144	91/68	81	141/85	109	128/78	100

femoral artery, however, showed a retardation of the upstroke of the pulse wave and a broad rounded peak, making the pulse contour almost a smooth curve. Figure 10 illustrates the contrast between the configuration of the brachial and femoral pulse waves in a patient of this series. The shape of the femoral pulse wave is the result of damping of each wave as it passes through the area of resistance presented by the aortic stricture and the collateral channels. It has been pointed out that the effect of the insertion of a small to moderate resistance into the pathway of a transmitted wave is to dampen the amplitude of the curve, leaving the mean pressure relatively unaffected.[25] It is by this mechanism that femoral pulse pressure is reduced while mean pressure remains at or near normal levels.

Prolongation of the normal interval between the onset of the upstroke of the femoral and the brachial pulse waves has also been reported.[23] Similar observations were made in the patients of this series. It may also be seen in Figure 10 that the duration of the femoral arterial upstroke was more than

twice that of the brachial. Since the sum of the entire length of the pulse wave is the same for both brachial and femoral arteries, the downstroke component must be shortened in the femoral.

Analysis of the physiologic data. An analysis of the mechanisms of hypertension from the data presented must deal primarily with the relationship of vascular resistance, blood flow, and blood pressure. Since the cardiac output of patients of this series is normal, the hypertension must be due to an increase in vascular resistance. This could be the result of one of two mechanisms. The first mechanism was suggested by Blumgart, who believed that the site of resistance was in the aortic stricture and collateral vessels.[7] The second mechanism, proposed by Steele,[12] by Stewart,[26] and by Rytand,[13] postulated that the increase in resistance was generalized, affecting the whole peripheral vascular tree. Such a disturbance exists in renal and in essential hypertension. Rytand is of the opinion that in coarctation the kidney is responsible for the increased resistance because of interference with its blood supply.[13] If this were the case, the overall arterial resistance exclusive of the stenosis and the collaterals should be elevated. However, calculation of an increase in overall peripheral resistance is not in itself sufficient evidence of a renal pressor mechanism, for in renal hypertension the resistance must also be equally distributed. By contrast, the increase in overall resistance which may be present in neurogenic hypertension produced by sectioning of the buffer nerves in dogs is of unequal distribution.[27] Therefore, if the hypertension in coarctation is renal, the increase in arterial resistance must affect all branches of the circulatory tree to an equal degree.

The resistance due to peripheral arterial tone alone may be estimated by subtracting from the total overall resistance a calculated value for the resistance of the stenosis and the collaterals. Let *rc* represent the resistance through the collaterals and the coarctation; R_T, the total overall resistance; and RP, the resistance due to peripheral aterioles alone; then

$$(1)\quad RP = R_T - rc.$$

With a simplified version of Poiseuille's formula $\left(\text{Resistance} = \frac{\text{Pressure}}{\text{Flow}}\right)$ the various resistances may be estimated.*

$$(2)\quad rc = \frac{PL}{F}$$

where rc represents the resistance through the collaterals and the coarctation; PL, the loss in pressure head across the coarctation and the collaterals; and F, the blood flow through the coarctation and the collaterals. Since it is not possible to ascertain the blood flow through this region, let F equal cardiac output. The rc thus derived then should be the lowest possible resistance for this portion of the vascular bed. Thus, R_T, the total overall resistance, would

* All resistances calculated by these formulae are expressed in arbitrary units.

represent the highest possible value, and RP would likewise be maximal.

$$(3)\quad R_T = \frac{PA}{F}$$

where R_T represents the total overall resistance, including that of the coarctation and the collaterals, PA the mean pressure in the brachial artery, and F equals the cardiac output.

Table II illustrates that preoperative and postoperative values for the peripheral resistance exclusive of the stenosis and the collaterals are below normal. Since these values are maximal, true peripheral resistances must be

TABLE II.—*Peripheral Resistance in Coarctation of the Aorta*

	Preoperative			Postoperative		
Case	R_T*	rc*	RP*	R_T*	rc*	RP*
B. A.	39	26	13			
V. W.	41.5	26	15.5	38.5	6	32.5
J. W.	49.5	18	31.5	17.5	1.5	16
R. K.	38.5	17.5	21	14	0	14
V. T.	33.5	11	22.5	36	0	36
A. P.	24	12	12			
D. B.	26	9.5	16.5	33	4.5	28.5
MEAN			19			25
NORMAL*			29			29

*R_T = total resistance including stenosis and collaterals = brachial pressure/cardiac index.

rc represents the resistance of the stenosis and collaterals $= \frac{>}{}$ drop in pressure/cardiac index.

R_p represents the peripheral resistance = R_T − rc.

Normal peripheral resistance calculated using a mean pressure of 96 mm. Hg and a cardiac index of 3.3.

lower. This finding differentiates the mechanism of hypertension in coarctation from that in renal and essential hypertension.

Further evidence for the absence of a renal mechanism in the pathogenesis of hypertension in coarctation is lack of proportional increase in resistance in various portions of the vascular tree. In an attempt to assess the resistance in various parts of the body, Steele[12] and Stewart[26] postulated an increase in the arteriolar resistance of the leg on the basis of an elevation of the diastolic pressure in the femoral artery. A similar increase in resistance was demonstrated in patients of this series despite the finding that only one out of 15 preoperative cases showed an increase in femoral diastolic pressure. This calculated increase in resistance accounts for the decrease in blood flow through the leg in the presence of a normal mean pressure. It is apparent from preceding discussions that conclusions regarding peripheral vascular resistance drawn from the height of the diastolic pressure alone are unjustified.

It is of interest that following the operation the blood flow through the leg approaches normal. (Figs. 7 and 11.) During the postoperative period of observation, however, there is a proportional rise in the mean pressure in the femoral artery, indicating that the postoperative resistance in the leg remains elevated. (Fig. 11.)

Blood pressures from the brachial artery obtained in the patients of this series agree with those of King, Steele, and others.[22, 12] Figure 9 illustrates that brachial systolic, diastolic and mean pressures are elevated. The blood flow through the arm is markedly increased (Figs. 6 and 11), and consequently the mean resistance is normal or only slightly elevated. (Fig. 11.) On the other hand, in patients with essential and renal hypertension the arm flow is normal but the vascular resistance in the extremity is markedly elevated. Postoperatively the blood flow through the arm and the brachial arterial pressure decrease in the same proportion. Therefore, no appreciable change in the vascular resistance occurs.

There is general agreement that the vascular resistance in the kidney is increased in patients with coarctation.[28] As in essential and renal hyperten-

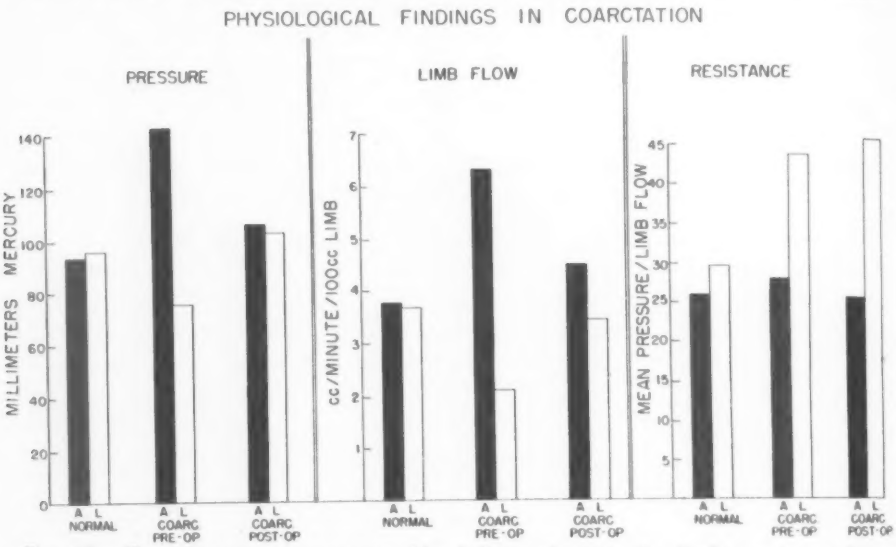

FIG. 11.—Compares mean pressures, blood flows through the limbs, and vascular resistance through the limbs before and after operation.

sion, the increased vascular tone is in the efferent arterioles. On the other hand, cases with severe hypertension in the upper extremity have been reported in which the coarctation was below the level of the renal arteries. In one of these, studied and explored at this hospital, the renal blood flow and the glomerular filtration rate were normal, but the vascular resistance in the leg was increased.[16]

Several findings in this report cast doubt on the theory that the hypertension in coarctation is the result of an increase in the peripheral resistance mediated through renal mechanisms. Estimated values for the overall arterial resistance exclusive of the coarctation and the collaterals are below normal. Furthermore, the existing peripheral resistance is unequally distributed. Since the resistance in the extremities is not lowered, other parts of the vascular bed must accommodate an increased blood flow. Investigations are in progress to determine the site of lowered vascular resistance. Finally, the increase in

the height of the diastolic pressure observed in both the upper and lower extremities, which has been used as evidence for increased arteriolar tone, can be readily explained as a result of damping of the pulse wave by the coarctation and the arterial collaterals.

SUMMARY

Twenty-three patients with coarctation of the thoracic aorta have been operated upon.* Thirteen of the patients were 20 years of age or above, while ten were younger. An anastomosis was completed in 21 cases of the 22 in which it was attempted. In 17 cases the stenosis was resected and an anastomosis of the proximal and distal ends of the aorta was performed. In four cases in which the proximal segment of the aorta was too short for end-to-end suture, the left subclavian artery was used to by-pass the stenosis. There were three deaths in the series, including one in a child who had multiple congenital defects which had been recognized preoperatively.

Physiologic investigations disclosed no significant deviation of the cardiac output from normal. Blood flows through the arm, which were elevated before operation, fell following surgery. The blood flow through the leg rose postoperatively. Hypertension in the upper part of the body and hypotension the legs was observed preoperatively. After operation, these pressures tended to equalize. Analysis of the physiologic data indicated no generalized elevation of peripheral vascular resistance. It is probable, therefore, that the hypertension in coarctation of the aorta is not attributable to a renal pressor mechanism, but is due to the resistance of the stenosis and collaterals.

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* Seven additional patients with coarctation of the aorta have now been operated upon. End-to-end anastomosis was carried out in all these patients and there were no additional deaths. Of these seven patients, one was 41 years of age.

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DISCUSSION.—DR. CLARENCE CRAWFORD, Stockholm, Sweden: First of all I should like to express my gratitude for the opportunity of being present at this meeting and taking part in this discussion, which I feel is a great honor. From the excellent results we have just heard from Dr. Blalock and his co-workers, and from my own experience, I think we may state that radical treatment of coarctation of the aorta can no longer be considered as a surgical equilibristic procedure; I think it can be said that it is a sound surgical procedure. The results I have had support the conclusions which can be drawn from Dr. Blalock's presentation.

We have now operated on 32 cases of coarctation; 31 of those were resected and

in one case we did a "Blalock operation" with anastomosis, end-to-side, between the subclavian artery and the aorta below the coarctation. In this series of 32 cases we had two postoperative deaths, one due to acute bleeding on the afternoon of the day of operation, the other due to formation of a dissecting aneurysm which broke into the bronchial tree, for the patient died a month after operation because of massive hemoptysis.

In addition to the 32 cases operated upon, we have explored five cases intending to try radical operation, but conditions were such that an anastomosing operation was not possible. These cases were in the older age group, between 25 and 35 years of age. In all, arteriosclerotic changes of the walls of the arteries were present, which made surgical intervention on the vessels impossible. In that group of five cases, which were explored and sutured again, we had two deaths shortly after operation. Because of that I would like to point out the value of a method of investigation that we have developed recently in the attempt to make as accurate an anatomic diagnosis of the lesion as possible before operation. We have introduced an ordinary cardiac catheter through the radial artery, pushing it forward down into the aortic arch. With the rapid injection of 50 to 70 cc. diodrast we can get an excellent x-ray picture of the first part of the aorta and the coarctation. I hope that, as we become more familiar with this method of investigation, we may be able to exclude most of the unsuitable cases from exploratory thoracotomy and select in advance those on which we may hope to achieve a good result.

(slides) In this picture you can see the catheter passed down into the arch of the aorta to the level of the aortic ostium. The curved outlines of the aortic valves are shown, and also a fairly good picture of the coronary arteries. We hope in the future to be able to carry out studies on the coronary arteries by this means. In the cases on which this procedure has been carried out, we have had no reaction which would contraindicate continuance of the method.

The second slide shows a case which was rather difficult to interpret. It was one of the first upon which this investigation was done, and we did not know how to interpret the different shadows. We therefore explored to confirm our x-ray findings, and in this drawing is shown what was found. There were multiple aneurysms on the aortic arch which made radical procedure of any sort impossible.

We have been able to follow 27 of the 32 cases for a period ranging between three months and three and a half years. Of the remaining five, two died in the immediate postoperative period, as mentioned, and three have been operated upon so recently that it is too early to tell how they will progress. In 13 of the 27 cases the blood pressure has returned to normal, with higher pressures in the legs than in the arms. In six, the blood pressure is equal in the legs and the arms and, in eight, it is still slightly higher in the arms than in the legs. In these eight we have not been able, from an anatomic viewpoint, to perform a sufficiently wide anastomosis.

In three cases of the 30 surviving there has been development of small postoperative dissecting aneurysms, demonstrated by direct aortagraphy after operation. Two of the three are symptomless; they have not been growing. In one case there are signs of increase in the size of the aneurysm, the patient has symptoms and we are discussing the possibility of reoperation.

The principal difference between the technic described by Blalock and Gross and the one I use is that both Blalock and Gross use everting sutures. I have felt that one should try to resect as much as possible of the constricted area, which is nearly always so long that it is difficult to resect enough. Because of that, I have used an anatomic suture with coaptation of the different layers of the aortic wall against each other, which permits resection of a few millimeters more than if an everting suture is used. I also feel that healing will be better and stronger when the different anatomic layers of the aorta are in direct contact. I do not know whether Dr.

Blalock and Dr. Gross have had postoperative aortagraphs made, or if they have found any postoperative symptomless aneurysms. A comparison between our series in that respect might give some indication as to whether the anatomic or the everting suture is to be preferred.

The mean blood pressure before operation in my cases has been 180/100 in the arms and about 100 mm of mercury systolic in the legs. After operation, the pressure in the arms has returned to normal, as mentioned above.

Dr. Egbert H. Fell, Chicago: I am sure we all appreciate this most extraordinary discussion by Dr. Crafoord. We all realize the great contribution made by Dr. Blalock and the impetus he has given to this new field of surgery. After spending a good deal of time in the laboratory and in attempting to operate on these cases, one realizes the great problems surmounted by Dr. Blalock, by our two new members, Dr. Gross and Dr. Potts, and by Dr. Crafoord, and it is their unselfishness and graciousness that has made it possible for those of us who are interested in the subject to carry on as we could not have done otherwise.

The purpose of this discussion is to present two cases to emphasize the fact that the most desirable time for operation is in childhood; first, because it is technically much easier and, second, because there are few or no irreversible reactions taking place in a child. Following such surgical procedures, these patients with very dark futures should be converted into normal or nearly normal individuals.

(slides) In the Presbyterian Hospital laboratories the technic as described by Gross was first carefully carried out in dogs. The success of these experiments encouraged us to attempt the procedure for the benefit of the boys to be described. These two children presented themselves in the pediatric cardiac service at Cook County Hospital about the same time for study. After Dr. Benjamin M. Gasul and his associates had completed their studies, they were transferred to the surgical service. The boys, 10 and 13 years of age, were well developed and healthy in appearance, but on questioning them and their families the following essential points in their histories obtained: Weakness after slight exertion; headaches and tachycardia, particularly the older boy; epistaxis, discomfort and coldness in legs on exertion; marked limitation of activities. Orthopnea was of great concern to the 13 year old and his parents.

These complaints were associated with hypertension in the head, neck, and shoulder girdle with low blood pressure in the rest of the body. No femoral pulse or blood pressure was elicited in either boy's lower extremities. The oscillometer readings were negligible; there was 3 to 7 degrees lower temperature of the skin of the toes to that of the fingers. X-rays of the chest showed notching of the ribs. Angiocardiograms revealed a stenosis at the isthmus of the aorta.

A successful operation was performed on the 10-year-old boy. The 13-year-old boy was operated on three days later. The procedure was more difficult because of his well-developed chest and shoulders and the tremendous collateral circulation in the chest wall.

In the first case the stenosed area was just distal to the junction of the arch of the aorta and subclavian artery at the attachment of the ligamentum arteriosum. The arch was clamped and the subclavian artery temporarily tied with a Penrose drain. The modified Potts' clamp as used by Dr. Blalock would have aided greatly in this case. The distal end of the aorta was clamped with a modified gastrointestinal clamp. The end-to-end anastomosis was completed with 5-0 silk, using a continuous mattress suture. The stenosis in the second case was approximately 2 cm. below the left subclavian artery, which was also stenosed in its first inch as it arose from the aorta and accounted for the 40 mm. of mercury of systolic blood pressure difference in the right arm over that of the left arm. The end-to-end anastomosis was carried out as suggested by Gross. Both boys have made satisfactory recoveries.

I should like to ask Dr. Bing if the eyegrounds were studied, and also what

kidney function tests other than blood flow were made in these cases. We hope to do that in the cases we now have at hand.

Dr. Norman E. Freeman, San Francisco: Dr. Blalock has just presented a fine series of cases and his results have been remarkable. There were two patients in his series, I believe, in whom the aortic lesion was found to be inoperable. I should like to mention a method for visualization of the aorta which may be of help in selection of cases for operation. This technic is quite similar to that so beautifully demonstrated by Dr. Crafoord.

Fariñas of Havana, Cuba, described a procedure for catheterization of the abdominal aorta through the femoral artery. Subsequently, he injected the contrast medium in a retrograde fashion directly into the femoral artery. With sufficient force, visualization of the abdominal aorta and its branches was obtained. Dr. Earl Miller of the Department of Radiology and I became interested in this technic of retrograde arteriography and, in November, 1946, had occasion to use it for visualization of the thoracic aorta. The patient was a woman of 26 with hypertension, who was admitted on the service of Dr. Howard C. Naffziger for surgical treatment. The resident staff noted absent femoral pulsations and, accordingly, the diagnosis of coactation of the aorta was made. Dr. Naffziger referred the patient to me for operation. There was, however, very little collateral circulation about the upper thorax, no notching of the upper ribs by x-ray and no murmurs over the precordium or paraspinal region between the scapulae. There were dilated collaterals about the lower thorax, umbilicus and flanks and a systolic murmur was audible in the region of T^{12} posteriorly and in the epigastrium. Injection of a contrast medium in retrograde fashion into the left common carotid artery demonstrated a normal thoracic aorta. The exact site of the coarctation was not definitely visualized but the x-ray examination proved that the narrowing was not in the usual location. Subsequently, Dr. H. Brodie Stephens, Dr. Mary Olney, Dr. Miller and I, with the help of the house staff, have developed a simple technic for retrograde arteriography, which has now been used in 14 patients in whom the diagnosis of coarctation of the aorta was suspected. The results in this series were reported last month before the American College of Physicians.

Under general or local anesthesia the left common carotid artery is freed up for a distance of 5 cm through an incision above the left sternoclavicular joint. It is surrounded by a segment of rubber tubing. With the patient lying flat on his back, preliminary films are taken and then a needle is inserted into the carotid artery and directed toward the aorta. This needle is connected by a short segment of rubber tubing to a syringe containing 70 per cent diodrast. In children, a No. 18-gauge needle is used and 10 to 20 cc. are injected. In adults we have found that a No. 16 needle is preferable with 50 cc. of solution. With the distal carotid temporarily occluded by rubber tubing, the solution is injected as rapidly as possible and serial x-ray films are taken. After exposure of the films the diodrast remaining in the left carotid is aspirated back into the syringe. By means of this technic we have obtained visualization of the aorta and its branches. The site of the coarctation of the aorta has been established in 11 cases. In three patients it was demonstrated that for various reasons, operative correction was not indicated.

Dr. John C. Jones, Los Angeles: We have operated upon 13 patients for coarctation of the aorta and completed some type of anastomosis in all. The end of the subclavian was anastomosed to the side of the distal aorta in two patients. The coarctation was resected and the end of the subclavian was anastomosed to the end of the distal aorta in two instances, and in nine patients the coarctation was resected and an end-to-end anastomosis of the aorta completed. The ages of these patients ranged from two and one half to 31 years. There were 2 deaths in the series. One was a 31-year-old male with a large heart who had been decompensated for two years. He had advanced arteriosclerosis and, after we were able to complete

a satisfactory anastomosis, the posterior wall of the aorta at the site of the proximal clamp developed a leak on removal of the clamp. This was repaired with some difficulty, but he died suddenly on the ninth postoperative day of a dissecting aneurysm, well proximal to the anastomosis, which was intact at autopsy. The other death was a male of 17 years in whom we had no difficulties in resecting and completing an end-to-end anastomosis, but he died suddenly four hours after operation, presumably of a leak or rupture at the site of anastomosis.

The seven survivals of the resection with end-to-end anastomosis of the aorta have had excellent results, with blood pressures in their legs as high as if not higher than in the arms. The two patients in whom the end of the subclavian was anastomosed to the end of the distal aorta likewise have been excellent results. The two patients in whom the end of the subclavian was anastomosed to the side of the distal aorta are improved, but the results might be estimated as only fair.

We have operated upon three patients of 5 years or younger; one was two and one-half years old and his, incidentally, was the easiest operation from a technical point of view. He had the smoothest postoperative course and he was able to go home on the tenth day after operation.

Since the collateral circulation is well developed early in life in these individuals, the indications are to operate upon them early. We have employed a variety of methods in our end-to-end anastomoses of the aorta, but at present prefer the use of four everting stay sutures combined with four running over-and-over sutures in the four quadrants.

DR. H. B. SHUMACKER, JR., New Haven, Conn.: Dr. Crafoord's very interesting discussion of the excellent paper by Dr. Blalock and Dr. Bing prompts me to describe briefly some experimental observations upon arterial suture which my associates and I have recently carried out. We have compared the results of end-to-end arterial suture performed by various suture technics, principally the everting mattress suture which Dr. Blalock has used and the direct anatomic layer-to-layer approximation which Dr. Crafoord has employed. Histologically, one gained the impression that the direct anatomic repair resulted in nicer repair, but functionally there was no doubt that the everting mattress technic was superior. When specimens were removed at varying intervals after suture it was evident that complications such as stricture, dehiscence, and the formation of small aneurysms at the site of suture were much less common when everting mattress sutures had been used. There was no significant difference in the incidence of thrombosis with the two methods. We were led to the conclusion that the everting mattress technic was preferable.

We also tested the breaking strength and the ability to withstand intraluminal pressure at varying intervals after end-to-end arterial suture. The recently sutured vessel will pull apart with little force but rapidly gains in strength, approaching normal values in a few weeks. Such repaired arteries withstand without bursting or leaking intraluminal pressures far in excess of systolic blood pressure even a few hours after repair, and within two weeks they withstand without difficulty pressures as high as or higher than do adjacent normal segments of the same artery.

DR. R. J. BING, Baltimore (closing): Dr. Blalock and I would like to congratulate Dr. Crafoord on his beautiful work. In addition, we would like to thank everyone who has participated in the discussion of our paper.

We are particularly interested in Dr. Crafoord's method of arterial angiocardiography. The method certainly appears to give beautiful pictures of the area of coarctation and seems worth while repeating in this country. The problem brought up by Dr. Fell about kidney function and coarctation has been examined at the Johns Hopkins Hospital by Dr. Genest and his co-workers. These investigators reached the conclusion that in many cases of coarctation the glomerular filtration rate is normal, while the effective renal plasma flow is decreased. These findings would indicate constriction at the side of the efferent arterioles.

THE PORTACAVAL SHUNT IN THE SURGICAL TREATMENT OF PORTAL HYPERTENSION

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THE RATIONALE of establishing an anastomotic shunt between the portal and caval systems of veins for the relief of portal hypertension has long been appreciated. In the belief that advances had taken place in surgery which may have a bearing upon the clinical success of portacaval shunts, Dr. Allen Whipple and I undertook a restudy of the problem in 1943.

This paper will be limited essentially to a discussion of the results in a series of 58 cases in which portacaval shunts were established. The operation was performed by either Dr. Whipple or myself in 48 of the series of 58 cases with a loss of 8 cases postoperatively. There were 11 postoperative deaths in the entire series. The cause of death in the eleven cases was as follows: Cholemia = 3 cases; cerebral damage = 2 cases; cardiac failure = 1 case; mesenteric thrombosis = 3 cases; shock from intraperitoneal hemorrhage = 1 case; gastro-intestinal hemorrhage = 1 case.

Space does not permit a critical analysis of each of the eleven postoperative deaths but a short discussion is timely.

In one of the three cases dying of cholemia, necropsy examination revealed liver cell degeneration compatible with an active virus hepatitis. Whereas there were also present periportal fibrosis and esophageal varices (the man had hemorrhaged once); nevertheless it was an error in judgment to have brought him to operation at the time, and, for the following reasons: (1) Recent (3½ mos.) history of virus hepatitis; (2) persistence of anorexia, exhaustion, jaundice and ascites; (3) persistence of a four plus cephalin flocculation test, reversal of the serum albumin-globulin ratio (albumin 1.9%, globulin 4.4%); and an elevated prothrombin time (50% of normal). We operated upon this case early in our experience, but we now know that we should have waited until evidences of active hepatitis had disappeared.

A second case who died of cholemia was that of a 59-year-old man having Laennec's cirrhosis of the liver complicated by tertiary syphilis. This patient in spite of a 9 months' trial of a dietary liver regimen, remained in a state of chronic liver decompensation with wasting ascites. Throughout this period his serum albumin gradually fell from 3% to 2.4%. There was no improvement in bromsulphalein excretion-retention which remained at 40% one-half hour after injection. Over much of the time cephalin flocculation tests were three and four plus, galactose removal constant and prothrombin times were 50% of normal. Though the serum phosphatase was, on most examinations, slightly elevated, the serum bilirubin remained normal. The decision to operate in this case was further influenced by the presence of demonstrable esophageal varices. A splenorenal type of portacaval shunt was established in this case. On the third postoperative day he became comatose and on the fourth day he died.

We now believe that the above described case might have survived the portacaval shunt procedure if for several weeks prior to operation, carbohydrate and protein feedings had been forced to the limit, using if necessary, intravenous albumin to help lessen the ascites and edema. Cyclopropane

*Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

instead of ether anesthesia would, in our opinion, have given him a better chance. Though admittedly his liver function studies classify him as a poor operative risk, we have two cases who survived portal vein to venacava anastomoses who were strikingly similar. Both cases became ascites free following operation. One of the patients gained 50 lbs. in weight and continues his work as a timber cruiser now 3 years since operation. The other case survived a strangulated hernia operation two months following the portacaval shunt procedure and carried on ascites free for 1½ years. At this point the patient became somewhat stuperous and the tongue became beefy red. One month later, he developed ecchymosis with the appearance of bloody ascites and a prolonged prothrombin time. During the third month of progressive liver failure, the course was rapidly downhill. There was a terminal rise of the blood urea nitrogen to 63 mg.%.

The third postoperative death assumed to be due to cholemia in the series was that of a 47 year old man who first entered the Presbyterian Hospital in 1940 with virus hepatitis. After a two months stay in the hospital the jaundice had cleared and the cephalin flocculation test returned to normal. Four years after the hepatitis the patient had his first attack of gastro-intestinal hemorrhage. In September 1947, the patient was readmitted to the Presbyterian Hospital stating that in January and July of that year, he had had episodes of hematemesis. Examination revealed an enlarged liver and spleen. The blood picture was that of Banti's syndrome. The cephalin flocculation and thymol turbidity tests were each three plus. The serum albumin was 4.3% and globulin 2.5%. Catheterization of the hepatic vein in this case revealed a 50% reduction in hepatic blood flow, with a high oxygen content but a 90% of normal extraction of bromsulphalein. These findings indicated the perfusion of considerable normal liver tissue with a high component of arterial (hepatic artery) blood. Roentgenograms revealed varices practically throughout the length of the esophagus.

The patient was considered a good liver risk for a portacaval shunt. On the 14th of October, 1947, he was operated upon. The liver was enlarged, irregularly nodular and firm. The gallbladder contained stones and the spleen was greatly enlarged. A splenectomy was performed and followed by a splenorenal shunt. Opening the shunt lowered the portal pressure from 370 to 270 mm. of water. A cholecystectomy was also done. The postoperative course of this patient until his death on the 29th day, well illustrates the ultimate seriousness of a cycle of complications in cases with liver damage.

The patient, starting out with the necessity of repeated catheterization and finally continuous catheter drainage because of an old urethral stricture, developed urinary tract infection. A bilateral pneumonitis followed and upon recovering somewhat from this, the patient developed phlebothrombosis of the femoral veins. Heparin therapy was instituted for this. Finally, on about the 16th postoperative day, the patient's temperature went higher accompanied by diarrhea and abdominal distention. This period was punctuated by gastro-intestinal bleeding. We considered strongly the diagnosis of mesenteric thrombosis at this point, but rather suddenly his abdominal distention and diarrhea ceased and his temperature went still higher. Two blood cultures were made at 9-day intervals. Salmonella Montivedio bacilli were recovered from each flask. During the last 10 days of the patient's life, he presented the picture of marked sepsis. The white blood count varied from 50,000 to 70,000 with the polymorphonuclears in excess of 90%. Some five days before death the patient developed a mild jaundice and two days before death, coma supervened.

We assumed that the above patient died of liver failure but it is of

interest that at six and two days before death, the serum albumin was 3.2% and 3% respectively. Unfortunately, no necropsy was obtained in this exceedingly interesting and complicated case.

The two postoperative deaths of the series in which cerebral pathology played a role are worthy of mention.

One a case of cirrhosis of the liver and lenticular degeneration of the brain (Wilson's disease). This 29-year-old man, during a year of observation upon an excellent liver regimen developed increasing signs of cerebral damage with an increased incidence of gastrointestinal bleeding. On the above account on September 10, 1947, a splenectomy and a splenorenal shunt procedure was carried out. Following operation, the temperature rose to 104°F. and was maintained at that level for 3 days. The patient became extremely euphoric and on the fourth postoperative day lapsed into coma. From this point until his death, two days later, his coma was punctuated with attacks of what appeared to be "sham rage".

Whereas slight jaundice did develop in the above case after the onset of coma it seemed unlikely to us that the coma was explained solely on the basis of a failing liver. His serum albumin which was 3.5% five days before operation fell to 3.4% two days after operation but was 3.6% the day before his death. We have not infrequently noted slight jaundice to develop in other cases a few days after operation in which multiple transfusions were employed. It seemed more likely to us that the cerebral pathology played a primary role in the coma in this case. Unfortunately, no necropsy was obtained in this case. At operation the large nodular liver with intervening scarring suggested the appearance of a liver following an attack of subacute yellow atrophy in which the surviving lobules have undergone hypertrophic enlargement. On microscopic examination the liver cells were frequently large and bizarre. The intervening scar tissue and liver capsule were infiltrated with lymphocytes with an occasional eosinophilic leucocyte.

The hepato-lenticular syndrome (Wilson's disease) is poorly understood. The course of the disease is usually rapidly downhill, and from what I can learn, they are inherently poor operative risks.

The second cerebral death in the series was that of a 23-year-old woman who had multiple arteriovenous shunts between the splenic artery and vein. As evidence of portal hypertension, there was a history of repeated hematemesis. At operation following removal of the spleen, the portal pressure fell but did not return to a normal figure. Accordingly, a splenorenal shunt was done because it was thought that some inaccessable arteriovenous shunts remained. The operation was carried out under cyclopropane and with minimal blood loss. The blood pressure was at no time below 100 systolic during the procedure and the patient was well oxygenated during the period. The first indication of a cerebral accident in this case was failure of the patient to wake up promptly and become responsive following cessation of the anesthesia. Although, a few hours later the patient could be aroused and answered questions, there were unmistakable neurologic findings of a cerebral accident. Her condition rapidly became worse and death occurred on the second postoperative day.

A complete autopsy revealed the anterior and middle cerebral arteries on the right to be filled with blood clot with extension of the clot into the right carotid artery. Careful search revealed no source of embolus. There were no septal defects in the heart. The splenorenal anastomosis was free of clot.

The mechanism by which blood clot became deposited in this young woman's cerebral arteries remains unexplained. She was given the usual dose of heparin when the portacaval shunt was opened and had a satisfactory rise in the blood clotting time. The heparin was given some thirty minutes before the anesthetic was stopped and it seems illogical that a thrombosis could take place, after the administration of heparin. If the accident is to be explained on the basis of a thrombosis, it must have occurred earlier in the operation.

Cardiac failure was the cause of death in one case.

A 64-year-old widow entered the Presbyterian Hospital on April 21, 1947, complaining of generalized weakness for 3 months and pain in the left side for 3 weeks. The patient gave no history of hepatitis. She rarely took alcoholic drinks. There was no history of hemorrhage, ascites or jaundice. On examination the blood pressure was 160/80. Roentgenogram showed an enlarged heart with a silhouette suggesting right and left chamber enlargement accompanied by left ventricular hypertrophy. On the other hand, the patient gave a negative cardiac history and the only heart finding on physical examination was a soft systolic blow at the apex. The prominent findings were an enlarged firm liver and a considerably enlarged spleen with a severe anemia of the hpyochromic type. The blood platelet and white cell count was markedly reduced.

Examination of the bone marrow was negative except for a slight increase in normoblasts. The prothrombin time was 18 seconds (normal 14 + 1 second).

The liver chemistry was as follows: Serum bilirubin faint trace; cephalin flocculation 3+++; serum phosphatase 7.1 Bodansky units; total protein 7.3%; albumin 3.9%; globulin 3.4%. The bromsulphalein liver function test revealed 90% retention 5 minutes after injection and 30% retention after one-half hour.

The electrocardiogram showed left axis deviation with evidence of myocardial damage. The gastro-intestinal series of roentgenograms showed diverticula of the colon. The intravenous pyelogram was negative.

On May 9, 1947, the patient was explored and the findings were as follows: The liver though enlarged was not nodular nor was the capsule thickened. The gall bladder was thick walled and contained calculi. The spleen was firmer than normal and approximately four times normal size.

Portal pressure proved to be 240 mm. of water. On the basis of our figures considered as normal, this represents a rise above normal of 130 mm. of water. Accordingly, a splenorenal shunt was done following removal of the spleen.

The patient did exceedingly well postoperatively for the first two days. The venous pressure ranged from 84 to 90 mm. of water. On the morning of the third postoperative day the temperature was 100.4° F., the blood pressure and pulse were satisfactory but a few coarse rales were heard at the right base and the venous pressure had risen to 127 mm. of water. The patient suddenly died in her sleep in the early morning of her fourth postoperative day, presumably of cardiac failure. No postmortem examination was obtained.

The above case has been presented in detail for the following reasons: (1) Examination of Microscopic sections taken from the spleen and liver showed infiltration of moderately immature cells of the myeloid series, as well as megakaryocytes. In the spleen the cells were found in foci within the germinal centers as well as in the pulp. Sections of the liver reveal foci of similar cells with a tendency to be found with greater regularity in the

portal spaces. The pathologist (Dr. W. Lehman) concludes in the absence of evidence of leukemia in the bone marrow examination and blood smears, that the diagnosis in this case is myeloid megakaryocytic hepatosplenomegaly. (2) Conceding myelofibrosis affecting mainly the portal areas of the liver to be an adequate cause of the portal hypertension and possibly the bromsulphalein retention in this case, the question now arises, should this patient have had only a splenectomy?

Of one thing we are certain. This patient should have been digitalized before coming to operation. It is our present policy to digitalize preoperatively all cases age 50 or over whose electrocardiograms show left sided ventricular preponderance. We now have several cases in their sixties who have gone through portacaval shunt operations successfully.

In the eleven postoperative deaths of the series of 58 cases, there were 3 cases who died of mesenteric thrombosis.

Case 1.—A 39-year-old woman who first entered the Presbyterian Hospital on May 30, 1946, complaining of weakness of five years' duration. On this admission, the patient was found to have a marked splenomegaly, secondary anemia, leucopenia and thrombocytopenia. A bone marrow examination was normal, revealing no cells typical of Gaucher's disease. The cephalin flocculation test was 4 plus. Serum phosphatase 2.5 Bodansky units. Serum bilrubin 1.5 mg. %. Total protein 6.2%. Albumin 3.8%. Globulin 2.4%. Bromsulphalein 90% retention 5 minutes after injection and 25% retention 30 minutes after injection. Serum cholesterol total 159 mg.%, free 36 mg.%, ester 123 mg.%.

A diagnosis of Banti's syndrome was made and the patient discharged for follow-up.

The patient was readmitted to the Presbyterian Hospital on September 7, 1947, unimproved. The liver chemistry studies were essentially the same as on the first admission, except that there had been a rise in the serum bilirubin to 2.2 mg.%. The secondary anemia and thrombocytopenia persisted. There had been no episodes of gastro-intestinal hemorrhage or ascites. Roentgenograms were negative for esophageal varices.

On September 25, 1947, the patient was explored. The liver was found to be the site of a diffuse uniform nodular cirrhosis. The spleen was enlarged about five times normal size. The portal pressure was found to be 400 mm. of water. A splenectomy was done and followed by a splenorenal type of portacaval shunt, end to side by suture. The liver biopsy confirmed the diagnosis of cirrhosis.

The patient ran a temperature to 101°F. daily during 17 days postoperatively. The platelet count gradually rose to normal over this period. Aside from slight ascites which quickly disappeared, there were no other important findings. After a 10-day period of essentially normal temperature, the patient began to have diarrhea and her temperature rose to 102°F. daily. The patient complained of low backache and lower abdominal tenderness. Examination revealed a flat abdomen with no marked tenderness. On pelvic examination on the left side, extending laterally to the left and posterior to the vagina, was a tender sausage-shaped mass. On rectal examination the mass was posterior and to the left of the rectum.

The patient's fever continued. The white blood count rose to 23,000 with 91% polymorphonuclears. A culture of the urine was negative. A stool culture yielded Salmonella Tennessee. Her temperature failed to respond to sulfadiazine, penicillin or streptomycin. The abdomen remained essentially soft following the onset of the diarrhea on the 27th postoperative day until the 43rd postoperative day when abdom-

inal distension rather suddenly became extreme. During the last few days of life, the patient became comatose and died on the 45th postoperative day.

The postmortem examination was of extreme interest in this case. The mass noted on pelvic examination on the 30th postoperative day proved to be a thrombosed hemorrhoidal vein. Gram negative rods were present in the thrombus which is of interest in that during the period of diarrhea bacillus, Salmonella Tennessee was recovered on stool culture. At necropsy examination the thrombus was found to have extended to include the inferior mesenteric, superior mesenteric and portal veins including of course the splenorenal anastomosis.

Case 2.—The second case of death from mesenteric thrombosis postoperatively is that of a 36-year-old man who was admitted to the Presbyterian Hospital on September 16, 1946. He presented the history of attacks of abdominal cramps followed by bloody diarrhea on two occasions, the first attack 10 years previously. Five months prior to admission there were two episodes of hematemesis. The physical examination finding of note was the presence of an enlarged spleen.

Laboratory studies were as follows: Barium enema roentgen rays were normal. Roentgenogram of the esophagus following a barium swallow showed varices. Stool cultures revealed no enteric pathogenic organisms, no ova or protozoa were found in the stools. Cephalin flocculation tests were 3 plus and one later 1 plus. Serum albumin was 3.9%; globulin 3.1%. Serum phosphatase 2.2 Bodansky units %. The prothrombin time was normal. The galactose tolerance test (intravenous) showed a removal constant of 2. as indicative of liver damage. The blood picture was that of Banti's syndrome, namely secondary anemia, leucopenia and thrombocytopenia.

The patient was explored on November 14, 1946. The liver appeared grossly normal but the spleen was approximately five times normal size. The portal pressure measured 340 mm. of water.

A splenectomy was done, followed by a nephrectomy and an end-to-end anastomosis of the splenic vein with the renal vein by the non-suture vitallium tube method.

Microscopic sections of the spleen revealed the usual picture of congestive splenomegaly. The sections of the liver biopsy revealed areas of slight liver cell degeneration, much pigment but no evidence of specific liver disease.

Following operation, the patient developed pneumonitis complicated by abdominal distension necessitating the passage of a Miller-Abbott tube on the second postoperative day. By the fifth postoperative day the distention of the abdomen had been relieved and the Miller-Abbott tube withdrawn. On the eighth postoperative day the temperature had subsided to normal. The patient had been actively up and about when he suddenly developed abdominal cramps with a return of the abdominal distention. Two days prior to this anticoagulant therapy (heparin) had been stopped. On the eleventh postoperative day abdominal cramps and distention had become markedly worse with the appearance of ascites. The temperature and pulse rate began to rise and on the thirteenth postoperative day the white blood count was found to be 37,000 with 90% polymorphonuclears. The platelet count had risen to 192,000.

A paracentesis was done on the thirteenth postoperative day. 2600 cc. of faintly turbid yellow fluid was removed. Whereas a culture of the fluid was reported negative, no examination of the fluid was made for the presence of red blood cells. Following paracentesis though, the abdomen remained greatly distended, and a

sausage-shaped mass could be felt in the right lower quadrant which was thought to be a distended loop of ileum.

On the fourteenth and fifteenth postoperative days, the patient was obviously worse and vomiting had set in. The white blood count was 39,000 with 92% polymorphonuclear cells. The pulse rate had mounted to 130 per minute and the temperature fell precipitantly to below normal. On the sixteenth postoperative day the abdomen was explored. All of the jejunum except for the proximal 3 feet and all of the ileum except for the distal 4 inches were dark purple with thrombosed vessels in the mesentery throughout the affected area. The insidious onset led the operator to believe that thrombosis of the mesenteric veins preceded that of the arteries. A jejuno-ileostomy was performed following resection of the non-viable bowl. The patient was well supported by transfusions and he stood the operation well.

The patient was given penicillin and streptomycin following the bowel resection and for a few days seemed better. However his temperature began to rise from normal on the third postoperative day and in spite of the presence of a Miller-Abbott tube, dilated loops of bowel was shown by Roengen ray. The patient's blood urea rose progressively and on the sixth post-resection day be became jaundiced. Acidosis developed. After the administration of 400 mil. equivalents of sodium lactate, the patient's CO_2 rose from 25 to 35 volumes percent and the plasma sodium rose from 110 to 129 M.E. In spite of these attempts to correct the electrolyte imbalance, the patient lapsed into coma, the temperature continued upward to 104° F. The patient died on the tenth day following intestinal resection and the 26th day following the establishment of a splenorenal shunt.

The important postmortem findings in the above case were as follows: Peritonitis, fibrino-purulent, generalized; abscess, right lower quadrant; dissolution, anastomosis site of ileo-jejunostomy with leakage of intestinal contents into the abscess cavity. The liver in the gross and microscopic examination was free of cirrhosis. The pancreas on section showed thrombosis of the smaller veins. There were areas of fat necrosis in the surrounding mesentery and omentum.

The alimentary tract revealed numerous large varices in the esophagus without evidence of ulceration or recent hemorrhage. The stomach was distended with edema of the mucosa which was dotted with petechial hemorrhages. The duodenum was also distended. The large intestine appeared normal.

The portal venous system was extremely interesting. The lumen of the portal vein had been replaced by interlacing white fibrous trabeculae which form a number of small canals. Under microscopic examination it was noted that these recanalized blood spaces within the portal vein were lined in part by endothelium. In addition two large rather recent thrombi were undergoing early organization with invasion of fibroblasts and capillaries at the site of attachment to the masses of fibrous tissue. Dark red thrombi were seen to extend into the splenic vein and superior mesenteric vein.

The above pathologic findings present the picture of cavernomatous transformation in all stages of recanalization including old organizing thrombus with extension of recent thrombus retrograde, throughout the portal radicals including the splenorenal shunt. What better nidus could there be for the

initiation of a postoperative mesenteric thrombosis! It seems logical that careful attention to the avoidance of postoperative distention and anticoagulant therapy properly administered will offer the best chances of preventing the formation of new thrombus in such cases in the future.

The third case of postoperative death due to mesenteric thrombosis was that of an obese middle aged woman having cirrhosis of the liver.

Following the establishment of a splenorenal shunt the operator decided to administer heparin hypodermically at six-hour intervals for some six or more days postoperatively. Toward the end of this period, the patient's abdomen became progressively more distended, ascites formed, she finally became jaundiced and died in cholemia. Necropsy revealed thrombosis of the portal vein with all of its branches including the splenorenal anastomosis.

In my opinion, pure heparin solution administered hypodermically at such long intervals as six hours apart may even predispose to the development of thrombosis at the site of a recently performed portacaval anastomosis. I base this opinion on recent unpublished observations made by Dr. Arthur Voorhees while working as a surgical fellow. Dr. Voorhees has done many highly accurate blood clotting determinations. He finds that in many people following the administration of a single dose of heparin, when the heparin effect upon the clotting time wears off, for an hour or more thereafter, the blood clotting time goes down to 50 or more per cent below the normal clotting time for that individual. We have found out that the best way to prevent this extremely undesirable effect is to administer heparin either intravenously in normal saline solution by a carefully controlled drip, or hypodermically at two-hour intervals.

The one death from shock due to intraperitoneal hemorrhage was solely the result of technical failure.

The case was that of a 54-year-old Cuban male who for one year had suffered from ascites due to portal cirrhosis of the liver.

Varices of the esophagus were demonstrated by roentgen-ray. The total serum proteins were 5% albumin, 3%, globulin 2%.

On August 15, 1945, the patient was operated upon. The liver was cirrhotic and extremely small. The portal vein was mobilized but upon mobilization of the venacava, the right renal vein was found to join the venacava extremely high. Accordingly the right kidney was removed and an end-to-end anastomosis established between the portal and renal veins employing the non-suture method. The abdomen was closed practically before it was discovered that a massive intraperitoneal hemorrhage had occured. On reopening the wound it was found that the hemorrhage had resulted from a torn omental vein which for a considerable period had gone unobserved. The shock from this additional loss of blood was calamitous for the patient and he failed to revive in spite of the quick administration of a large amount of blood and plasma.

The above death from hemorrhage due to faulty hemostasis occurred early in our experience. The case taught us much about operating in the presence of severe portal hypertension.

I report the eleventh postoperative death as representing a series of tragedies.

The case was that of a 47-year-old housewife who entered the Presbyterian Hospital with the complaint of three attacks of vomiting of blood during the two years prior to admission and swelling of the abdomen of three months duration.

The patient gave a negative history of exposure to hepatotoxins. Starting in 1935, the patient had an attack of nausea with loose bowel movements. There was no associated abdominal pain, fever, jaundice or vomiting. The identical attack recurred in 1941. Between August and October of that year, the patient had 9 attacks. In none of them was there any abdominal pain or jaundice. A cholecystogram revealed the presence of gall stones and in October, 1941, the gall bladder was removed. For a 9-day period following operation, the patient was jaundiced. From 1941 until the time of her first hematemesis (July, 1946) the patient had been free of symptoms. During the attack of hematemesis much blood was lost but there were no other prominent symptoms. Three attacks of massive gastro-intestinal hemorrhage occurred over the ensuing two years. Ascites and edema of the lower extremities appeared following an attack of bleeding 3 months prior to admission.

Physical examination revealed a pale, somewhat obese woman who presented the following pertinent findings; namely, a very large spleen, a large firm liver, and some ascites and pitting edema over the sacrum.

The laboratory findings were as follows: Serum bilirubin negative; serum phosphatase 4.4 Bodansky units %; non-protein nitrogen 17 mg.%; total serum proteins 6.5%; albumin 3.9%; globulin 2.6%; cephalin flocculation 3 plus; thymol turbidity 3 plus. Bromsulphalein 50% retention 5 minutes after injection and 25% 30 minutes after injection. Prothrombin time 17.3 seconds (normal 14 plus or minus 1 second). A gastro-intestinal series of roentgenograms revealed the presence of esophageal varices. The intravenous pyelogram was negative. The red blood count was 3,240,000 hgb. 9. Gm.; WBC 6.450. Platelets 106,000; reticulocytes 2%. Blood clotting time 20 minutes (Lee White method).

At operation the patient got a bad start, having a persistent nosebleed following the introduction of the intratracheal tube. When the skin incision was made, hemorrhage from minute vessels warned us of a bloody procedure. In view of this fact it was thought wise to set up for an arterial transfusion. Accordingly, a cannula was introduced into the right radial artery at the wrist and a transfusion started. The spleen was removed through a left thoraco-abdominal approach. The spleen was adherent to the diaphragm and some six times normal size. The liver was large, firm and nodular on the surface. The patient's extreme tendency to bleed made the problem of hemostasis terriffic and greatly complicated and prolonged the procedure.

Finally, after removing the spleen and mobilizing the plenic vein stump, we exposed the left kidney and encountered another difficulty; namely, subcapsular hemorrhage. The kidney was completely mobilized, brought forward and compressed by a gauze pad. An end-to-side splenorenal anastomosis was performed by suture technique, but upon returning the kidney to its bed it was noted that subcapsular hemmorhage had spread to the point of necessitating a nephrectomy. The stump of the renal vein distal to the anastomosis site was repaired following nephrectomy. The patient left the table in remarkably good condition having received 5000 cc. of blood via arterial transfusion. The case was a supreme test for this method of administering blood and the blood pressure was maintained magnificently throughout the procedure.

At this point, I want to call attention to a serious complication of arterial transfusion that was evident in this case at the conclusion of the operation; namely, ischemia of the fingers of the hand. As the result of the use of a glass cannula in the right radial artery at the wrist, it was necessary to

ligate the radial artery at this level. In this particular case there was congenital absence of inosculating branches between the ulnar and radial arteries, and gangrene of the second, third and fourth fingers and tip of the thumb resulted. The necessity for ligation of the radial artery in this case could have been prevented by the use of a baby Lindeman needle.

Aside from the above mentioned complication, the patient's condition was satisfactory for the first 24 hours after operation. It was noted on the second day, however, that her respiration and pulse rate rose sharply. The latter were labored with marked laryngeal stridor. Laryngoscopy and bronchoscopy revealed blood clot between the vocal chords and a large plug completely obstructing the left bronchus. Removal of these obstructions gave temporary relief but atelectasis of the left lung recurred, the patient again became cyanotic and laryngeal stridor returned. The rapid heart rate and rising temperature were ominous. Tracheotomy was done following which another large plug was removed from the left bronchus. Whereas the left lung became aerated, the temperature remained high as well as the respiratory rate. On the fifth postoperative day, the patient's white blood count was 24,000; hgb. 8 Gm.; RBC 3,200,000. The blood pressure had dropped precipitantly from 130 systolic to 100 and the pulse rate had risen to 140 per minute. Hemorrhage was suspected and transfusions started. The patient's blood pressure was boosted for a time with three transfusions but finally, on the sixth postoperative day, she again went into shock and died.

Necropsy examination confirmed the clinical impression of hemorrhage in this case. The stomach and intestines were filled with blood. No exact site of bleeding from the esophageal varices could be determined. The splenic vein up nearly to the site of the splenorenal shunt was the seat of a recent (24-hour) thrombus. The actual anastomosis was noted to be free of thrombus. There was some fat necrosis of the tissues surrounding the pancreas suggesting trauma to the tail of the pancreas at operation. The liver was dotted with nodules and on microscopic examination showed the picture typical of Laennec's cirrhosis.

Many complications might have been avoided in this case if before operation she had been properly prepared with transfusions. The last preoperative blood count done the day before operation showed 3,160,000 red blood cells and 9.3 Gm. of hemoglobin. In my opinion, the great tendency to bleed in this case was more on the basis of her anemia than of thrombocytopenia. It is now our policy not to operate on cases with severe Banti's syndrome until the hemoglobin has been brought up to 14 Gm. and the RBC to 4,000,000.

We accept this case as one of technical failure, though the actual anastomosis site was not thrombosed.

The eleven postoperative deaths in the series of 58 cases of portacaval shunts have been presented in some detail to illustrate some of the many factors involved in the successful handling of this type of case.

Upon reviewing the cases, one or more serious errors are noted in eight of the eleven cases as follows: Of the cholemic group, the case with active hepatitis obviously should not have been operated upon. Another case was

poorly prepared for operation and should have received cyclopropane anesthesia. It was perhaps an error in judgment to have operated at all on the case of cirrhosis with lenticular degeneration (Wilson's disease). Failure to digitalize preoperatively the case who died of cardiac failure was certainly a serious omission. Two of the three deaths from mesenteric thrombosis involved factors beyond the operators' control but in the third case, in my opinion, an error in judgment in the way heparin was administered postoperatively may have been a contributing factor to the initiation of thrombus formation. In the two cases of death from shock secondary to hemorrhage, certainly errors in judgment and technical failure were directly responsible. I refer to the case dying of massive gastro-intestinal hemorrhage and the case dying of intraperitoneal hemorrhage.

The obligations of surgeons who would undertake a series of portacaval shunts are twofold: (1) To accomplish the operation with a reasonable expectancy of survival of the patient. (2) To employ a surgical technic and routine of postoperative handling that will insure a high percentage of maintained patency of the portacaval anastomoses.

The follow-up histories in our series are dotted with what must be accepted as failures in the sense of the total prevention of the recurrence of hemorrhage.

Of 35 cases who gave a history of severe attacks of gastro-intestinal bleeding before the establishment of portacaval shunts, 11 have had one or more attacks of hemorrhage following discharge from the hospital. The follow-up time ranges from a few months to three or more years.

Analysis of these 11 cases reveals that five of the cases had previously had splenectomies. Four of the five cases had extrahepatic portal block making it unfeasible, as we have routinely found by experience, to employ the portal vein in establishing a portacaval shunt. The types of portacaval shunts established in these four postsplenectomy bleeders were as follows: stump of splenic vein, end to side, with the venacava equals one case; proximal end of inferior mesenteric vein with the venacava, end to side equals one case; superior mesenteric vein to venacava, side to side, equals one case; superior mesenteric vein, distal end to side of the venacava, equals one case.

In the one post splenectomy bleeder in which the cause of the portal hypertension was due to cirrhosis of the liver, the distal end of the portal vein was bridged to the venacava, end to side, employing a vein graft-lined Vitallium tube.

In patients with extrahepatic portal block who have had their spleens removed at previous operations the surgeon is usually limited, as in the above cases, to the choice of employing either the proximal stump of the inferior mesenteric vein or the superior mesenteric vein. The former vein is often so small that even if the anastomosis remains patent, the shunt does

not handle enough blood to furnish absolute protection against he recurrence of attacks of hemorrhage.

Because of the many branches and other anatomic disadvantages it is exceedingly difficult technically to accomplish a side to side anastomosis of the superior mesenteric vein with the venacava. In my opinion it was an error in judgment on the part of the surgeon to have anastomosed the distal end of the superior mesenteric vein to the venacava as previously cited. It is not reasonable to assume that there are sufficient anastomotic branches below the point of section of the superior mesenteric vein connecting with branches proximal to the point of section appreciably to lower the pressure in the coronary vein. Branches of the latter vein inosculate with branches of the esophageal vein and it is the pressure in this vein with which we are primarily concerned in the prevention of hemorrhage from esophageal varices. In this connection it is interesting that the case in which an end-to-side anastomosis of the superior mesenteric vein to the venacava was employed, an attack of hematemesis promptly followed discharge of the patient from the hospital.

Further analysis of the eleven cases whose follow-up history has been complicated by the recurrence of gastro-intestinal hemorrhage is of interest. The splenorenal anastomosis was destroyed by the development of a low-grade infection in one case—the subdiaphragmatic collection of pus on the left was drained some months later. One case was readmitted to the hospital with gastro-intestinal bleeding shortly (2 months) after the establishment of a splenorenal shunt by suture. The patient was in extremis upon her second admission and failed to respond to blood transfusions. Necropsy revealed evidence of bleeding throughout the gastro-intestinal tract. The splenorenal anastomosis was patent. The liver was enlarged and nodular. The common duct was completely filled with small calcium bilirubinate stones. Microscopic sections of the liver revealed the presence of extensive biliary and portal cirrhosis, esophageal varices were present. The true cause of this patient's unremitting, painless, jaundice of some five years duration was not established before or at the time of the splenorenal anastomosis and, to make matters worse, she received no hykinone injections following discharge from the hospital. One can only say in retrospect, that if the common duct obstruction had been relieved first, the patient might now be alive. There is little doubt that portal hypertension was a contributory factor in this patient's attacks of hematemesis over the years prior to admission to the hospital, the portal pressure readings were found to be high. The case stresses the importance of first carefully ruling out obstructive (surgical) jaundice and the necessity of Vitamin K administration in such cases.

The nonsuture method, employing vitallium tubes, was used in six of the 11 cases. The anastomoses have been proved to be closed in two. In five cases the suture technic was employed and in one, a two-year-old child, the anastomosis is proven closed. The above trend in favor of suture anastomosis

fortunately occurred early in our series. As a result, in the large majority of the series of 58 cases operated upon the suture method has been employed.

Early in our experience we became fully cognizant of the many pitfalls in this procedure of establishing portacaval shunts both as to survival of the patient and the successful maintenance of patency of the shunts. For the above reason we have been exceedingly careful in dictating our operative notes in regards to the condition of the veins anastomosed, errors in blood vessel technic etc.,—factors that could possibly influence the continued patency of the anastomoses. In the 11 cases that have given a follow-up history of bleeding it is not surprising, therefore, to find, upon reviewing the operative notes, how frequently technical errors of omission or commission were made. For example, in one case who has had one episode of bleeding during the year following operation, I find in the operative notes that there was a palpable thrill upon opening the anastomosis due to slight twisting of the splenic vein. Though attempts were made to fix and hold the vein in an untwisted position by the placement of fine silk sutures, nevertheless the thrill did not entirely disappear.

Assuming that one could routinely accomplish the perfect suture anastomosis, there yet remain factors which can influence the outcome in regards to sustained patency of the anastomoses. Granted that one can prevent or control postoperative distension or, with anticoagulant therapy, control blood clotting over the three or four day period of endothelialization of the suture line, there yet remains the factor of the normality of the veins anastomosed. The latter we consider one important factor that should influence the operator's decision as to the type of portacaval shunt to employ.

In our series of 58 cases there were 16 cases in which the portal hypertension was secondary to extrahepatic, portal block. In such cases our experience so far, because of the high incidence of involvement of the portal vein, has led us to depend primarily upon the splenic vein for the establishment of a portacaval shunt.

In 42 of the 58 cases the cause of the portal hypertension was intrahepatic. In such cases the portal vein to venacava type of portacaval shunt can usually be employed. As to the question of which type of portacaval shunt:—the splenic vein to renal vein, or the portal vein to venacava anastomosis, has the highest likelihood of remaining permanently open, in my opinion the odds favor the latter. In the first place the portal vein, due to its thicker wall, will withstand years of portal hypertension without undergoing any appreciable degenerative changes that may effect the success of an anastomosis. Such is not the case with the inherently thin-walled splenic vein. The latter is often found to be greatly dilated with sacculated areas in which the wall is thinned out. Areas of sclerosis with intimal plaques are encountered and, in some instances, areas of reduplication of the intima.

In the splenic vein many pancreatic branches are encountered which, when ligated and cut, become promptly filled with clot. This clot in itself contributes a nidus, which, under certain postoperative conditions, may serve to initiate thrombus formation. The portal vein, however, near the site for the anastomosis, is essentially free of tributaries. In an end-to-side anastomosis with the venacava, for example, usually one, and never more than two tributary ligations are necessary. And, in case a side-to-side anastomosis is done, with the use of a special clamp, it is possible to complete the operation without ligating a tributary of the portal vein.

Last but not least in importance, is the anatomic setting in relation to the choice between the splenorenal and the portal to venacava types of portacaval shunt. In the first place, unlike thick-walled arteries, which carry blood under high pressure, the portal radicals are thin walled and are subjected to changes in intra-abdominal pressure following the establishment of portacaval shunts far in excess of the intravascular pressure. For the same reasons, the portal vein is thicker than the splenic vein and its anatomic relations are not such as to make it as subject to compression by contiguous organs or tissues as occurs upon completion of the splenorenal shunt. The tail of the pancreas, for example, will so frequently flop over and obscure the anastomosis upon repositioning the kidney at the very time one is most interested in getting a final glance at the splenic vein and the anastomosis. The colon, in turn, is nearby, ready, with the slightest over-distension, to compress the tail of the pancreas against the anastomosed splenic vein lying directly beneath it. If one resects the tail of the pancreas, the mass sutures required to effect hemostasis inevitably leaves behind more devitalized tissue which, in turn, results in the formation of scar tissue adjacent to the splenic vein. Late contraction of this scar tissue introduces the hazard of constricting the splenic vein.

Finally, in the end-to-side anastomosis of the splenic vein to the renal vein, one is somewhat concerned by secondary contracture of scar tissue about the splenic vein in its retroperitoneal course to reach the renal vein.

How frequently fat necrosis occurs following trauma to or resection of the tail of the pancreas, I am not prepared to state. The pathologist reported the finding in one postoperative death—the case who died of gastro-intestinal hemorrhage.

By comparison, the portal to venacava type of portacaval shunt is singularly free from most of the aforementioned hazards. Though appreciating long ago the likelihood that the portal to venacava anastomosis has the best chance for permanent patency, we have proceeded with caution in its use.

In the series of 58 cases we have employed the venacava to portal vein anastomosis nine times, with one postoperative death. We now have a follow-up of three years in three cases and nearly three years in a fourth. In these long follow-ups on these four cases we have noted no essential differences in the behavior of their cirrhotic livers, either clinically or chemically, from

that of comparative cases upon whom we have employed the splenorenal shunt. One of the cases developed diabetes and attacks of dizziness some two years following operation. The dizzy attacks have occasionally been accompanied by momentary loss of consciousness. Thorough neurologic examinations have failed to explain the attacks except that there is evidence of cerebral arteriosclerosis.

If one plans to do a portal vein to venacava type of portacaval shunt, a thoracic approach through the right diaphragm has certain advantages. For some two years this approach for complicated surgical problems of the liver

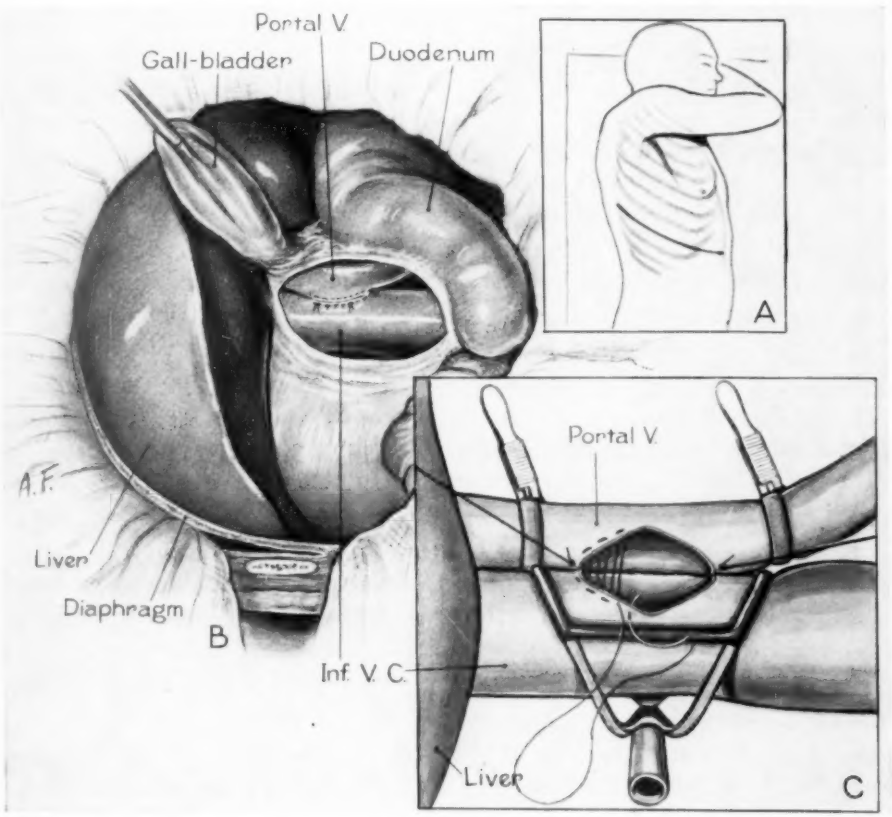

FIG. 1 (A.)—Shows the position of the patient on the operating table with the right side up. Note the incision over the ninth rib starts slightly beyond the posterior axillary line and continues obliquely downward and forward to cross the right rectus muscle to the midline of the abdomen. (B.) Illustrates a distinctly lateral approach to the hepato-duodenal ligament. The completed side-to-side anastomosis of the portal vein to the venacava is finally covered by suturing the cut edges of the peritoneum with a few interrupted sutures of fine black silk. (C.) Shows rubber covered clamps in place with the portal vein and venacava being anastomosed. The posterior half of the anastomosis has been completed employing a running everting mattress suture of #00000 braided silk. The posterior running suture is interrupted by tying to three stay sutures, two of which are illustrated. Note, that the transverse incision across the portal vein should extend two or three millimeters beyond the middle. This affords an anastomosis, which when completed, is slightly larger than the cross section area of the portal vein.

and bile ducts has been employed in our clinic with considerable satisfaction by Drs. Humphries and Heeney.

The primary advantage of the thoracoabdominal approach, with the patient lying on the left side, is a distinctly lateral approach to the hepatoduodenal ligament. With this side approach, the peritoneum can be incised directly over the portal vein and the latter dissected free without isolating the common duct (see Fig. 1). The pertoneal incision may be extended to curve laterally around the duodenum for a short distance to permit slight medial mobilization of the latter. The venacava is approached through an incision of the peritoneum directly over it anteriorly. Viewed from the lateral position after incision of the peritoneum, one is impressed with how much the venacava bulges forward—sufficiently, in fact, to touch the portal vein which, when it is freed, bulges backward somewhat to meet the venacava.

After employing the thoracoabdominal approach for the end to side anastomosis of the portal vein with the venacava and observing that the two vessels, after mobilization, touched one another, I have recently done one case anastomosing the portal vein side-to-side with the venacava. The designing of clamps that now permit one to do side-to-side suture anastomoses of the portal vein to the venacava on humans without the necessity of closing off entirely the flow of blood through the venacava, at long last makes the true Eck fistual procedure clinically practical. Figure 1 illustrates the completed side to side anastomosis of the portal vein with the venacava (see legend). Note that due to the fact that the portal vein does not run quite parallel to the venacava the incision has been made transversely in the portal vein for slightly more than half its diameter, whereas the incision in the venacava is more obliquely placed.

It is of interest that opening of the portacaval shunt in this case resulted in a drop in portal pressure to 330 m.m. of water from a previous level of 590 m.m. of water. This large drop in portal pressure represents an additional advantage of the larger portal vein to venacava shunt over the usually smaller splenorenal type of portacaval shunt.

The side-to-side portal vein to venacava anastomosis would seem to offer two possible theoretical advantages over the end-to-side variety, namely: (1) It permits portal blood flow through the liver should ever the pressure relations become conducive to flow; (2) A lessened tendency to thrombosis of the portal vein towards and into the liver. Fear of this more than any other single factor deterred us from using the end to side portal vein to venacava type of portacaval shunt more frequently. This fear was not unfounded, because the one postoperative death in the eight cases in which end to side anastomosis was done did have thrombus extension from the ligated portal vein. However, careful study of this thrombus suggested that it occurred while the patient was in extremis a few hours before death. This was the case of cirrhosis of the liver previously reported as dying of

liver failure secondary to virus hepatitis of recent origin in which evidence of active liver cell damage was still prevalent throughout the liver.

SUMMARY

In a series of 58 cases of portacaval shunt, eleven postoperative deaths are reported and discussed in some detail.

There were eleven cases in the series who have had one or more attacks of gastrointestinal bleeding following discharge from the hospital.

In 16 of the 58 cases the portal hypertension was considered to be secondary to obstruction in the portal bed outside of the liver. In 42 of the cases the cause of the portal hypertension was intrahepatic.

The different types of portacaval shunts are discussed and a technic is presented for doing side to side (Eck fistula) anastomosis of the portal vein with the venacava.

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DR. ALLEN O. WHIPPLE, New York: I cannot help but comment on several points. This is a veno-venous anastomosis and is quite a different problem in technic and repair from an arterial anastomosis or an arteriovenous anastomosis. The second point is that the blood pressure, fortunately or unfortunately, drops rather rapidly after anastomosis, which prevents high pressure flow to low over the suture line as one sees it in arteriovenous anastomosis. The third point is the observation made in one case which showed amazing regeneration of the liver following the shunt procedure. This young man was an alcoholic. He developed severe hemorrhage and a diagnosis of cirrhosis had been made before he came to us. It was a question whether he should be operated on. He had a high bromsulfathein retention and a 4+ Hangar test. We attempted the shunt and it was successful. Three or four months later he had an upper abdominal episode and was taken to St. Luke's Hospital and operated on for a perforated duodenal ulcer, and Dr. Adee made some interesting observations on the liver. At the time we operated he had had a marked cirrhotic liver. Dr. Adee found that he had large and small areas of regenerated liver tissue, such as is seen following subacute yellow atrophy. A month or two after that, while convalescing, he went down to Georgia, contracted a hepatitis with mild jaundice and yet survived that.

DR. DUDLEY ROSS, Montreal: I would like to commend Dr. Blakemore's figures on portocaval shunts, but was a little disappointed in his remarks with reference to the splenorenal shunt. At the Children's Memorial Hospital in Montreal we have been particularly interested in knowing whether splenorenal shunts were functioning or not, and for that reason I would like to present to you a suggested procedure for determining the patency of splenorenal shunts.

(slides) This slide shows a catheter introduced into the right median basilic vein, passed down the superior vena cava through the right side of the heart down to the inferior vena cava lying in the left renal vein. This is a patient who had been operated on one month previously for Banti's syndrome. The spleen, which was four or five times normal size, was removed. The pressure of the portal system at operation was found to be 250 mm. of water and the flow from the severed splenic vein appeared to be under pressure that was excessive. Careful search of the splenic vein was made for obstruction at the same time, but none found. The

anastomosis, end-to-side, was carried out and one month later the following test was done. Fasting sugar determinations were made from venous blood at various sites. As you see by the slide, the hepatic vein was 85.5 mg. per cent; the left renal vein was 69 mg. per cent; the inferior vena cava below the junction of the left renal vein was 72 mg. per cent. Then 100 mg. of glucose were introduced by means of the jejunal tube you saw in place in the previous slide, and ten minutes later further readings were taken from the left renal vein, which was found to be 166 mg. per cent and peripheral venous blood 150 mg. per cent. The catheter was left in situ. Ten minutes later another specimen showed 170 mg., in the left renal vein, 158 in the vena cava, and 164 in the peripheral venous blood.

There is no great difference in the fasting state between the vena cava and renal sugar levels, though the renal level is slightly lower. The hepatic vein blood sugar was considerably higher, presumably due to release of sugar from the liver. Following absorption of glucose from the duodenum we find a consistently higher sugar content in the left renal vein than in the vena cava or peripheral vein. We feel that this signifies the functioning of the anastomosis. It is impossible to tell, of course, how much of the portal load is being carried by the shunt, since the portal blood sugar level is not known. The figures, as I have said, indicate that in all probability the shunt is functioning. This child had visible varicies. We saw these varices by x-ray before operation, and they had subsided to a considerable extent, so far as x-ray showed.

This work was carried out by Drs. C. A. Allard, Eleanor Harpur and A. L. Johnson.

Dr. Arthur H. Blakemore, New York (closing): I want to thank Dr. Whipple and Dr. Ross for their discussions. I do not want to give the impression that we felt too blue about the splenorenal shunt. We sincerely feel that in many cases the shunts are still open. We have, by clinical comparison, a good deal of evidence that points that way. I am glad to see Dr. Ross's efforts, which look very encouraging, to determine whether or not the shunts are open. That is certainly very welcome. We are now undertaking some work in the same direction, passing a catheter down the vena cava and a tube in the intestine, in which we plan to put some radioactive iodine in the tube and pick up specimens of blood at different levels from the vena cava.

CLOSURE OF DEFECTS IN CARDIAC SEPTA*

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TORONTO, CANADA

THE HIGH INCIDENCE of defects in cardiac septa in 350 congenital hearts examined, about 50% being diagnosed as patent inverventricular or interauricular septa, stimulated my interest in the subject.

Only those defects in the septum which appear to be single lesions are included in this consideration. The perforated septum in tetralogy of Fallot, tricuspid atresia or patent ductus arteriosus and so on are not included and only those are considered when the septum is thought to be the predominant congenital defect and the one causing symptoms.

It is obvious that a small interventricular or interauricular septal defect, in the absence of infection, is of little or no significance. Cases are recorded where soldiers have gone through commando training and through the recent war with known congenital interventricular septal defects with no change in size of heart and no ill effects.

On the other hand, if the septal defect in either auricle or ventricle is large, it is possible that it may be the source of symptoms, and may be accompanied by cyanosis. The symptoms and the cyanosis may depend on several factors, but perhaps the size of the opening is one of the most important, which opinion is supported by Toussig[1] in her recent excellent book on Congenital Heart Disease.

The cases to be considered for operation in my view are those in which the heart is not excessively enlarged; the septal defect is not too large, such as occurs with a single ventricle, and before the patient has reached maturity. On the other hand, they may not be suitable for operation when there is evidence of an enormously enlarged heart with failure, and perhaps a single ventricle instead of a medium sized defect in the septum. I found on post mortem examination of congenital hearts, when a patient has survived to the age of medium childhood or the early twenties, has some cyanosis, has a moderate amount of energy, but with a moderately enlarged heart, that there has been an opening in the interventricular septum of perhaps one to two or more centimeters, in diameter.

In the few cases I have operated on, I was impressed with the high pressure in the pulmonary artery. This on measurement with a monometer was about equal to that of the pressure in the aorta. Whether that high pressure is the result of the septal defect or whether it is accounted for by some congenital anomaly in the pulmonary vascular tree, I do not know. Neither do I know whether this high pressure is reversible if the hiatus in the septum is closed. However, it seemed worth while to attempt to close the hiatus, presupposing that this might be the source of the high pulmonary artery pressure. I have a suspicion that there is some abnormal physiology

* Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

in the pulmonary vascular tree which may not be remedied by closure of the septal defect alone. For this reason, the problem did not lend itself well to animal experimentation because the septal defects produced artificially in animals were not accompanied by long standing pulmonary hypertension.

Animal experimentation, however, did give us practice in operating on the heart. We learned how much the heart could be manipulated and displaced from its usual position, and its response to stimuli and to transfixion with foreign bodies. With practice, we were able to locate the position of the septum, from the surface markings on the anterior and posterior surfaces of the heart. Using this information we were able to pass needles and probes through the heart anteroposteriorly in the plane of the septum, and place ligatures, crossing artificially formed defects, in the interventricular and interauricular septa. We could see danger signs and learned to judge their significance, and how to relax and rest the heart so that its abnormal responses to stimuli were soon overcome and the circulation was maintained. We were able to proceed with what appeared to be relative safety.

Then came the problem of applying this principle to congenital septal defects in human hearts.

The problem resolved itself into:

(1) A consideration of the different reactions which might occur in the human heart when compared with an animal heart.

(2) Secondly, and probably most important, was an anatomic consideration of the area involved, to know what to do, what not to do.

My objective in the interventricular defect was to pass a suture, of considerable size on cross section, through the heart from front to back so that it would pass across the defect in the septum. It was hoped that by slight compression of the heart from before backwards, by this suture, the hiatus could be diminished somewhat in size. Secondly that the substance of the fairly massive living suture would in itself obstruct the hiatus to a degree. If one suture could be passed, then perhaps two or more could be passed in such a way as to interweave them and give fairly complete occlusion of the hiatus. This, accompanied by some local thrombosis, and healing of this area might, with good luck, cause sufficient obstruction of the hiatus to improve the function of the heart and relieve the patient of symptoms.

ANATOMIC CONSIDERATIONS

(1) The decending branches of both the right and left coronary arteries are described as passing down in the interventricular sulci anteriorly and posteriorly. These sulci are described in anatomy books as roughly outlining the anterior and posterior margins of the septum. Also, the transverse branches of both left and right coronaries run transversely in the auriculo-ventricular sulcus and these again, are in the field of operation. It was necessary then to go carefully into the anatomy of the heart to know more accurately what are the exact surface markings, of the anterior and

posterior margins of the septum, and so to know at what point in relation to the sulci and coronary arteries the septum can be approached with safety.

(2) The next anatomic structures in direct relationship to the operative field are the valves of the pulmonary artery and aorta anteriorly, and the tricuspid and mitral valves with their chordae tendineae more posteriorly. At the operation, it is necessary to pass the instrument and suture material down between these right and left series of valves so that none of them will be interfered with; so that the cusps are not caught in the suture material; so that the chordae tendineae and the papillary muscles are not caught in the sutures. Any serious interference with these structures would precipitate an immediate disastrous effect.

(3) The next structure to be avoided is the bundle of Hiss, or the conducting bundle which traverses the interventricular septum to reach the papillary muscles and ventricular walls.

These anatomic points will now be discussed in further detail.

The left coronary artery coming from the left sinus of Valsalva, courses toward the heart over a distance of about five-eighths to three-quarters of an inch. Reaching the anterior surface it divides into descending and transverse branches. The right arises from the right anterior sinus of Valsalva, courses distally to reach the posterior aspect of the heart, dividing into the right descending and transverse branches. In the books on the subject, these descending branches are placed in the anterior and posterior interventricular sulci.

To get more accurate information, Professor Grant and Dr. Mahanti dissected 15 hearts to determine the exact relationship of the septum to these surface markings. From within the heart, sutures were passed from both right and left surfaces of the septum, through the heart muscle, reaching the surface on both the anterior and posterior aspects. These sutures in a sense "staked-out" the margins of the septum as they reached the surface on both anterior and posterior surfaces and demonstrated the relationship of the attachment of the septum, to the anterior and posterior sulci, as well as to the descending branches of the coronary artery.

On the posterior surface, the interventricular sulcus corresponded to the attachment of the septum in six. The septum was attached to the left of the sulcus in nine and to the right in only one.

The descending vessels, both arteries and veins, were examined in relation to the septum. The septum was found to be attached to the left of the vessels in eight, over the line of the vessels in five and to the right of the vessels in two.

On the anterior surface, the descending branch appeared to lie more closely in relation to the sulcus than it did in the posterior, and the relationship to the septum was slightly more constant. It was demonstrated that if a point was taken to the right of the descending branch in front, and imme-

diately distal to the auriculo-ventricular sulcus, this fairly accurately marked out the attachment of the septum anteriorly. (Fig. 1)

If with an opaque medium, a defect in the interventricular septum should be demonstrated at a more distal point, such as occurs in the Rogere type, then suitable points in this corridor, both anteriorly and posteriorly would give a direct approach to the site of the defect.

Regarding the valve rings in the annulus fibrosis or skeleton of the heart, there are many diagrams in Quain's, Gray's, Cunningham's, Grant's

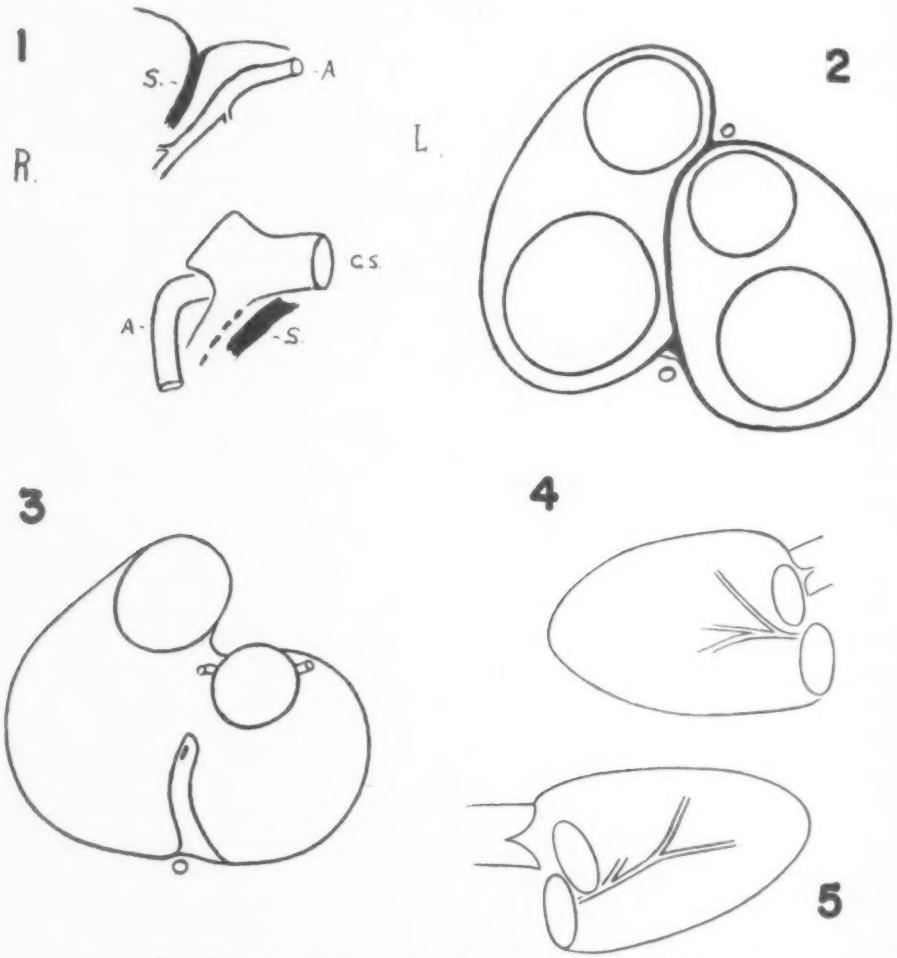

FIG. 1. *Top* S—septum, upper end seen from front and, A—coronary artery anterior descending branch. Showing relationship of upper end of septum to artery. *Bottom* S—septum A—descending branch right coronary, C S—coronary sinus. Showing relationship of septum to these structures on posterior surface of ventricles.

FIG. 2.—Diagram of annulus fibrosis with ventricles removed, showing valve seats and the relationship of the attachment of the base of the interventricular septum between the right and left groups.

FIG. 3.—Diagram of annulus fibrosis and the attachment of the base of interventricular septum in the presence of a patent septum.

FIG. 4.—Course of Bundle of Hiss seen from left ventricle.

FIG. 5.—Same—seen from right ventricle.

Atlas, Buchanan's and in many of the anatomies. To get further details, we did many dissections, again with the assistance of Professor Grant, as well as in the postmortem room, and Figure 2 represents our impression of what we found in relation to this. On looking at the diagram it is rather disconcerting to see that the attachment of the base of the septum to the annulus fibrosis, between the pulmonary and aortic valves anteriorly, and the tricuspid and mitral valves posteriorly, is curved. However, we have found practically, that to follow this line and place a foreign body or suture, in this line, is not as difficult as might appear, especially is this so when there is a hiatus and consequently the curves are not present. (Fig. 3.) The other problem which arose in placing such a suture was the possible presence of a dextraposed aorta. So far picking up the annulus fibrosis between the aortic and pulmonary rings in order to seal off completely the right margin of the dilated base of the aorta which is seen in Eisenmenger's disease has not been accomplished. However, with a suture well placed, it was hoped that it might provide useful occlusion.

There probably is more of a safety margin between the mitral and tricuspid valves than might appear on theoretical consideration. The septal cusp of the mitral valve when open, does not lie closely against the interventricular septum, but the septal cusp of the tricuspid lies more closely to the septum during diastole. (Fig. 2.) The attachment of the chordae tendineae to papillary muscles leaves a moderate space, probably up to half an inch, between them, through which there is room to work with little danger. We have had little difficulty in passing this area.

(3) Regarding the bundle of Hiss, there are many excellent dissections including those by Professor Grant and Dr. Mahanti, showing the course of this bundle. It arises posteriorly in the wall of the right auricle, traverses the annulus fibrosis and is directed forward and downward, posterior to, then below or, in the margin of, the membranous septum. In some congenital hearts, with a patent septum, the bundle was found to lie in the existing muscular portion posterior to the hiatus. At its origin it lies beneath the endocardium on the right side of the septum in the position indicated. As it passes distally beneath the pars membranacea septi, it divides into right and left bundles, the left passing through the substance of the muscular portion of septum to reach the plane beneath the endocardium on the left side of the septum from whence it courses to the musculature and papillary muscles of the left ventricle.

An instrument or suture passed through the heart, as described, necessarily crosses almost at right angles to the course of this bundle, and it, of course, must not be injured. The instrument and suture should pass in the direct line of the septum or slightly to its left to avoid the bundle as it lies beneath the endocardium on the right surface of the septum. Neither in our experimental work nor in the clinical patients operated upon, has there been evidence of ill effects produced by injury to the bundle of Hiss. Figure 4

shows and interventricular septum looked at from the left ventricular surface and No. V looked at from the right ventricular surface, indicating the course of the bundle of Hiss, in relation to the pars membranacea septi and the muscular portion of interventricular septum.

The interauricular septal defect also presents a challenge, but it is much less difficult to meet than is the interventricular defect, chiefly because the structures in relation to the field are easier to avoid.

Usually an interauricular septal defect is a persisting foramen primum and not foramen ovale. If giving symptoms or cardiac enlargement the defect is large. It causes ill effects by allowing left auricular blood which has just returned from the lungs to flow into the right auricle from which it again goes to the lungs with unsatisfactory completion of circulation. The ingenious method described by Cohn[2] of San Francisco has worked very well in experimental animals in their hands, and can be applied quite satisfactorily to small septal defects between the auricles. However, small septal defects probably cause few clinical symptoms, and their method would be difficult to apply in larger septal defects and in those in which the septum is practically missing.

In about 30 animals we have passed sutures through in the line of the interauricular septum beginning at the site of the transverse sinus behind the aorta, and coming out posteriorly between the superior vena cava and the right pulmonary veins. With two, three or four sutures through in this way, pulled taut, tied together posteriorly and then tied anteriorly, we have been able to compress the anterior to the posterior wall of the auricle in such a way as completely to occlude the defect. It has the other advantage of diminishing the size of the enlarged auricles. On examination of specimens, the anterior wall of auricles has healed to the posterior wall in such a way as to cause complete occlusion of the defect and construction of what appears to be another interauricular septum.

CASE REPORTS

Case 1.—C. G.: The first patient operated upon was a child of 17 months. There was fairly marked cynaosis and moderate clubbing. The child had not walked and had so little energy she would sit only when supported. The mother described a persistent cough and sputum, which was shown at operation to be related to atelectasis of the whole left lung. The heart was greatly enlarged. (Fig. 6.)

Operation. Cyclopropane was supplemented by continuous intravenous of one-tenth per cent novocaine solution. Exploration was made through the second left intercostal space down the middle of the sterum and out through the sixth space. On opening the pericardium one per cent novocaine solution was sprayed over the surface of the heart. A suture was passed through the apex of the left ventricle. Apart from extra systoles, there were no untoward effects. The heart was then dislocated forward and examination of the posterior surface carried out without difficulty. During this, the heart became more blue, and there seemed to be some embarassment of its action. However, on allowing it to return to its normal position, it recovered its poise and normal action. The heart was about two and one-half to three times normal size. It showed some cyanosis. The right

ventricle was enlarged and appeared to be roughly equal to that of the left. The pulmonary artery was greatly dilated and had high pressure; on palpation it felt equal to that of the aorta. The coronary vessels appeared normal.

A strip of fascia lata about three-quarters of an inch in width and six inches in length with a good blob of tensor fascia femoris muscle on the upper end, was removed. Through the other end a silk suture was attached. This was threaded on a straight sewing needle four inches in length.

A point was selected on the anterior surface of the heart, above and slightly to the right of the descending branch of the left coronary artery, just distal to the annulus fibrosis. Here, one per cent novocaine solution was injected, making

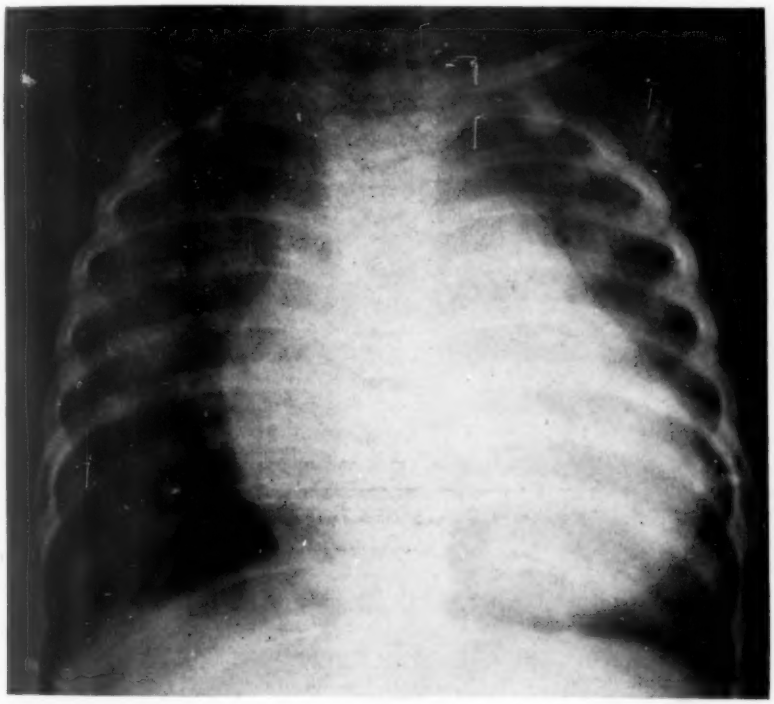

FIG. 6.—Rontgenogram showing size and shape of heart in child 17 months of age.

a bleb beneath the epicardium. With the threaded needle reversed, it was passed through the anterior wall of the heart, at the point mentioned. There were some extra systoles, but no other disturbance of the heart action. When the blunt end of the needle had passed through the wall of the heart, it felt as if it were in a cavity and not in the substance of the septum. On palpation with this needle, as with a probe, it was found to be in a fair sized hiatus measuring about 1.5 cm. It was passed across the hiatus until an obstruction was met at the posterior surface. Then on swinging the heart forward, by traction on the apex, and with the finger posteriorly, the end of the needle could be felt, like the end of a probe through the heart muscle posteriorly. The right position was then selected and the needle passed on through the posterior wall appearing through the epicardium. There was no injury to coronary vessels or coronary sinus. By the time this was completed, the heart became moderately cyanosed and showed some irregular action. However, on allowing it to go back into its normal position, with the needle

still through the heart, the heart regained its regular action and poise. The cyanosis which had appeared, diminished and the blood pressure remained normal. The needle was left in situ, through the heart for several minutes, to see if there was any interference with mitral or tricuspid valves, or any other ill effect. The cardiac conduction appeared to be normal. The needle was then drawn through posteriorly and with it the silk and living suture. Again this was held lightly in position, by slight traction on the posterior end, to observe any ill effects. If necessary we could, at any moment, remove the suture. However, there were no ill effects. Traction on the suture was increased, causing it to tighten across the hiatus, and almost immediately there was some improvement in the appear-

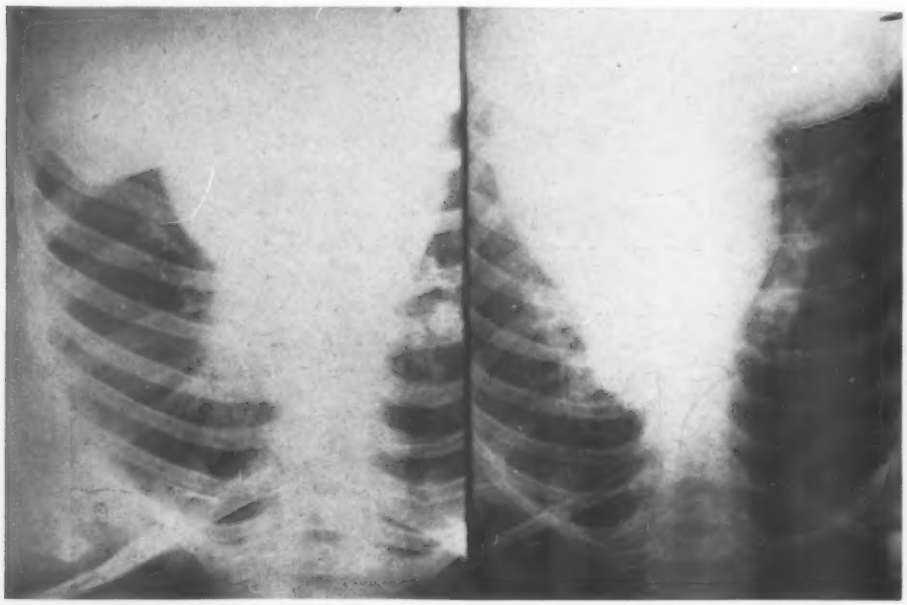

FIG. 7. Age 11—Patent interventricular septum.
On left—before operation.
On right—ten days post operation shows some inflammatory oedema at lung hilus, also change in size and shape of heart.

ance of the heart. Its size, particularly of the right ventricle, diminished quite considerably. The color of the heart improved and there seemed to be no ill effects. The anesthetist found no change in the patient's condition or blood pressure. It was thought, therefore, that perhaps the suture was in a satisfactory position and was performing some useful function. While moderate traction was applied to the posterior end of the suture, it was stitched to the epicardium at several points, avoiding branches of the coronary artery. This moderate tension caused some anteroposterior compression of the heart at the site of the hiatus. The mass of muscle in the anterior end of the suture, plugged the anterior opening in the heart satisfactorily. There was practically no hemorrhage and the patient stood the operation very well. The pericardium was repaired and the chest closed.

Case 2.—W. L., age 11: The patient was not cyanosed but had little energy. Examination showed an enlarged heart. He was operated upon through an exposure similar to the above. The heart was about three times normal size. A

living suture was passed through in a fashion similar to that described. The patient stood the operation very well. There were no ill effects whatever. On tightening the suture in position, there was marked diminution in size of the heart with improvement of its color. Blood pressure which was 120 systolic at the beginning, during the operation fell to 108, but by completion of the operation had returned to 120.

The patient made an uninterrupted recovery. On the fourth day he was given heparin for a period of seven days, keeping his clotting time between eight and 14 minutes. The result seemed to be quite satisfactory, although the late result cannot be determined as yet. Figure 7 shows the heart roentgenograms before and 10 days after operation.

Case 3.—BB., age 13: This patient was operated on quite satisfactorily with similarly good results.

Two other patients were explored hoping to carry out a similar procedure. However, in both of these, transposition of great vessels was discovered which had not been revealed with certainty by clinical, radiographic evidence or by catheterization of the heart. In these no interferenc with the heart was carried out.

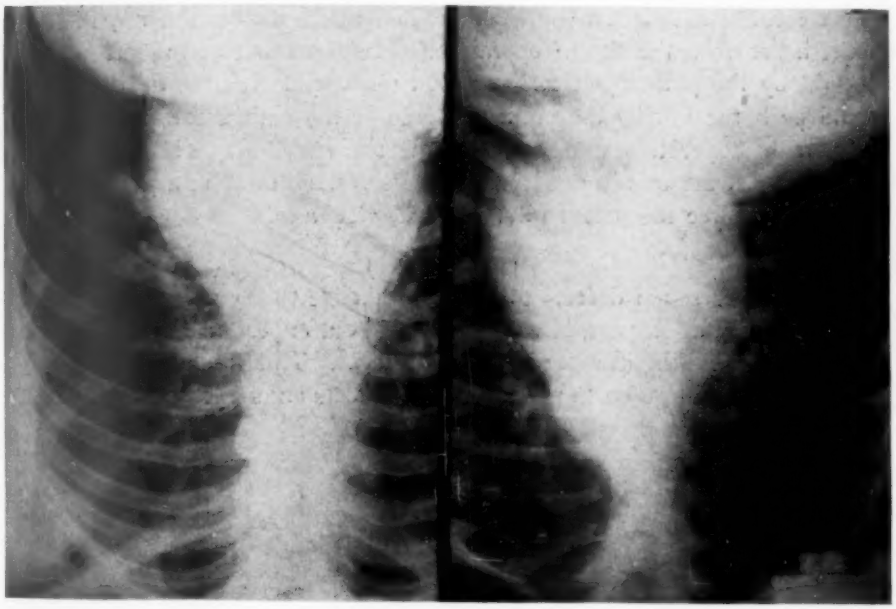

FIG. 8.—Patent interauricular septum.
On left—before operation.
On right—Two weeks following operation showing change in size and shape of heart.

INTERAURICULAR SEPTUM

Case 4.—C. W., age 12: This patient was operated upon through a similar exposure, for a patent interauricular septal defect as well as what was thought to be a smaller patent interventricular septal defect. At operation the right auricle was found enormously enlarged, probably ten times the size of the left. The auricular appendage was at least ten times as large as that on the left side. The ventricles, while enlarged, were small in comparison with the enormously enlarged right auricle. By means of the enlarged right auricle, the heart was already rotated very much to the left so that the aorta appeared on the right

side of the pulmonary artery. It was decided, therefore, to place our sutures of silk, in this case, beginning to the right of the aorta and pulmonary artery and emerging posteriorly through the area between the superior vena cava and the right pulmonary veins. Two sutures were passed through without difficulty. (It is the plan in future cases to pass more than two sutures.) These sutures were tied together posteriorly and were drawn taut from the anterior end and compressed with the finger. This caused a very great change in the size, shape and color of the heart. The right auricle diminished to at least one-half its size within about two minutes. The patient's general condition was good. The blood pressure remained normal. The sutures, after experimenting with this for some time, were tied down firmly, compressing the anterior and posterior walls of the auricles. This caused continued improvement in the patient's condition. The chest cavity was then closed without drainage. (Fig. 8.)

The patient made an uninterrupted recovery. From the fourth to the 11th day she was given heparin[4] to prevent propagating thrombosis from the area of suture. She made a good recovery and her general health is much improved. As there was very little cyanosis before, there was little improvement on this account.

One of these patients undergoing operation for interventricular septal defect died. Examination showed that the patient died not of any ill effects in the heart or at the site of operation. The atelectasis of the left lung was thought by the pathologist to have been responsible for the death, and this would be borne out by the clinical course of the patient toward the end of the first postoperative week, which time she survived. The suture going through the heart was in good position and seemed to be in a position to occlude to a degree the patent interventricular septum.

CONCLUSIONS

The cardiac septal defects present a challenge to the surgeon. Attempts at closure, at least in part, have been carried out experimentally, and in clinical patients resulting in moderate improvement. This would suggest further work which might go on to produce better effects anatomically and clinically. The demonstration that this can be done with safety is probably the chief feature of the present work.

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DISCUSSION.—DR. ARTHUR H. BLAKEMORE, New York: I certainly enjoyed this presentation. I heard via grapevine what was going on in Toronto and I congratulate Dr. Murray. Some years before the war, I think in 1939, we did some experimental closures of the septa in dogs, that we had made by a punch. We were rather interested in seeing how well simple inversion of the auricular appendage worked when pushed through the opening and, after getting it in there, packing in some fascia lata to make it a self-retaining ball on the other side of the septum.

I should like to ask Dr. Murray what kind of needle he used and also would like to know how tight he drew the interventricular septal sutures.

DR. ALFRED BLALOCK, Baltimore: You all remember the amazing paper on coronary occlusion presented by Dr. Gordon Murray at the last meeting of this Association, and now he comes forward with an even more amazing presentation. Certainly it never would have occurred to me to place sutures blindly in this manner. I did not understand, Dr. Murray, what type of suture you used other than that it was a living suture. I would like to ask further about embolism, if there has been evidence in your experimental or clinical work of that. I take it that a good part of the occlusion of such a septum is from the thrombosis which occurs on the suture material.

(slides) I would like to describe a new method for creating an inter-auricular defect. This method was devised by Dr. Hanlon and myself and the advantage of it is that it can be done under direct vision and without excessive blood loss. The ability to carry it out depends on the fact that the pulmonary vein is attached to the posterior wall of the right auricle. In this diagram you can see that part of the right auricle, together with the pulmonary vein immediately posterior to the auricle, is occluded by an especially devised clamp. An opening is made in the pulmonary vein and a similar opening in the right auricle. The posterior segment of the auricle is adherent to the anterior wall of the pulmonary vein, so one can simply excise a segment of the two walls; in fact, one can pull an additional quantity of this septum out and excise it. The closure consists simply of suturing the anterior part of the auricle to the anterior segment of the pulmonary vein, it being unnecessary, of course, to place any sutures posteriorly.

We have used this method on only one patient, and that only ten days ago. This was a child with transposition of the great vessels. The postoperative result is good thus far, although it is too early to know the eventual outcome.

Again I wish to congratulate Dr. Gordon Murray on his excellent work.

DR. D. W. GORDON MURRAY, Toronto (closing); Regarding Dr. Blakemore's discussion about needles, we use skin needles with the rough edges and the point removed, or ordinary seamstress needles of the larger variety. Wood needles for darning or for petit point work are good. Any of the needles are used in reverse, putting the eye through first, using it much as one would a probe. With this the front wall of the heart, then the hiatus, then the posterior wall can be felt quite satisfactorily.

Regarding the tension applied to the suture through the interventricular defect, it is pulled sufficiently that a bit of a dimple appears on the anterior wall where the knot on the end of the suture comes against the wall of the heart. By holding the end posteriorly, one can feel if anything else, such as a valve or chordae tendineae, may be tugging on it, much as a fisherman feels a bite on a hook in the water. If satisfactory, it is then stitched down to the epicardium front and back. In the one case examined at postmortem, the suture was in satisfactory position and seemed to be under satisfactory tension.

Regarding Dr. Blalock's question about the type of sutures: For the interventricular one, we use a living suture removed from the fascia lata of the thigh. This is of fair size, so that by its bulk it will partly fill the opening in the hiatus. While we have not used more than one, probably several could be applied to more or less produce a basket weave to more or less fill the hiatus.

For the inter-auricular septal defect, linen, cotton or silk sutures are used. With these the front wall of the auricle is drawn down and sutured to the posterior wall.

So far as embolism is concerned, this is controlled by the use of heparin. We hesitated to give heparin immediately. However, on the second or third day, heparin has been administered so that any thrombosis that might have occurred up to that time, would then be limited and allowed to heal in position. There has been no evidence of extensive or dangerous thrombosis, and no embolism in any of these patients.

REVASCULARIZATION OF THE HEART *

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CLEVELAND, OHIO

FROM THE DEPARTMENT OF SURGERY, WESTERN RESERVE UNIVERSITY AND THE UNIVERSITY HOSPITALS, CLEVELAND, OHIO. THIS INVESTIGATION WAS SUPPORTED BY A RESEARCH GRANT FROM THE DIVISION OF SURGERY, U. S. PUBLIC HEALTH SERVICE.

INTRODUCTION

IT IS AGAIN MY PRIVILEGE to present investigations on revascularization of the heart. The work done by us in the period between 1932 and 1942 has been reported. Briefly stated, we showed that the heart could be revascularized in two ways. One of these was by the production of extra coronary anastomoses, i.e., communications between the coronary arteries and the blood vessels of tissues grafted upon the heart. The other method for revascularization was by the production of communications between the various coronary arteries so that one artery connected with another. This was accomplished by the production of inflammation on the surface of the heart. These methods were effective to the extent of reducing by 50 per cent the mortality that occurred after ligation of the descending ramus of the left coronary artery at its origin. Thirty-seven patients with severe coronary artery disease were operated upon using these methods and the clinical results confirmed the experimental studies.

Since February 1945 my associates and I have been attempting to revascularize the heart by converting the coronary sinus into an artery. The results of this work up to February 1947 were recently published.[1] It is my purpose to present this work to this association. A number of investigators are now working on the coronary problem and no doubt our experiences will be an aid in their work.

DISCUSSION

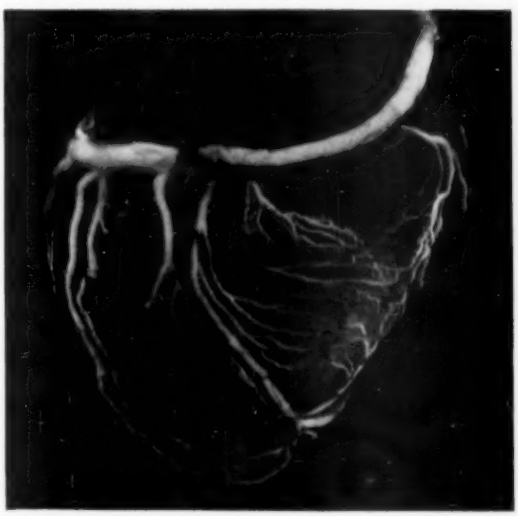
The coronary sinus. This is a vein that lies in the auriculoventricular groove of the left ventricle. (Fig. 1A.) It carries blood from the left ventricle and empties into the right auricle on the posterior aspect of the heart. The sinus can be ligated with little or no mortality. After it has been ligated blood drains directly into the four chambers of the heart. The sinus is then available and can be used for the entrance of oxygenated blood to the left ventricle. The wall of the sinus becomes thickened after it has been ligated. The sinus and its tributaries can tolerate arterial pressures.

The Artery for Anastomosis to Sinus in the Dog. The only artery in the dog that was large enough and long enough for anastomosis was the common carotid. We used the left carotid artery. It was dissected free throughout its course; it was transected below the bifurcation and it was turned down into the chest. The technique of anastomosis is shown in Figure 2.

New Branch from the Aorta. The common carotid artery is larger than the coronary arteries. No doubt it is larger than necessary. In man the

* Read before the American Surgical Association May 29, 1948, Quebec, Canada.

A



B

PLATE I. A.—Anterior view of human heart. Coronary sinus and coronary arteries were injected. The venous system is white; the arterial system is red.

B.—Posterior aspect of dog heart. Common carotid artery was used for anastomosis to coronary sinus. Carotid artery and coronary sinus injected in white; coronary arteries injected in red.

carotid artery frequently cannot be sacrificed without cerebral complications. In the dog it can be taken almost as a routine provided the bifurcation is preserved. The dissection of the carotid artery in a patient with coronary artery disease would add considerably to the magnitude of the operation. For these reasons it was necessary to consider other possibilities to obtain arterial blood. A pulmonary vein was considered but we did not believe the pressure was high enough in this vein to produce adequate flow. A new branch from the aorta appeared to be the best possibility. (Fig. 3.) The aorta lies in close proximity to the sinus. It is about three centimeters from the sinus. The

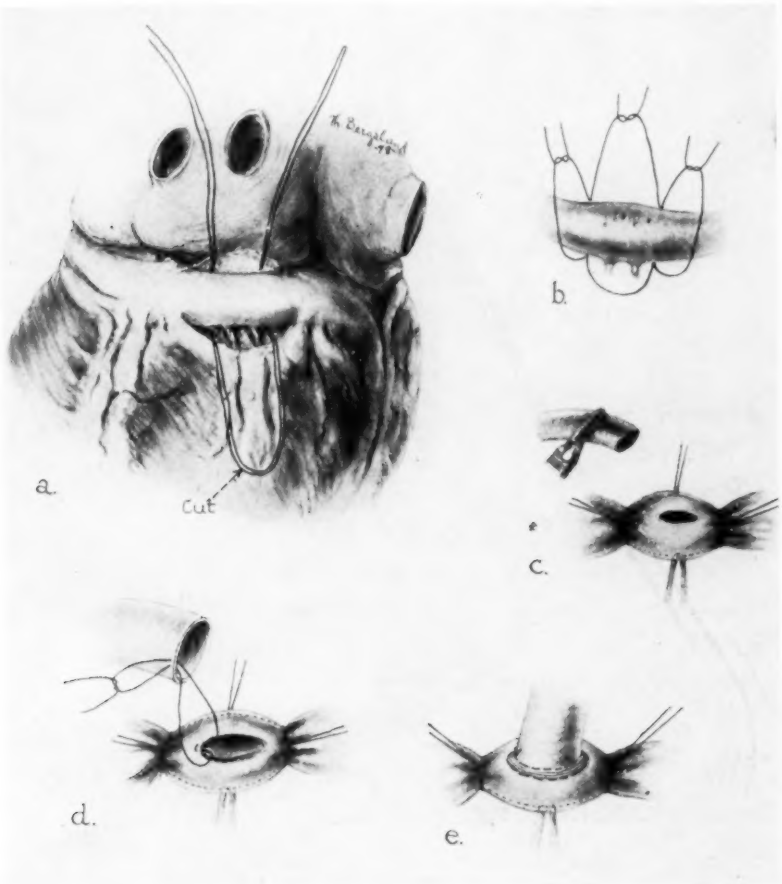


FIG. 2.—Anastomosis of left common carotid artery to coronary sinus in the dog. (a) and (b) show method for isolation of segment of sinus so that it can be opened without hemorrhage. The sinus is partially dissected free. A carrier with two silk sutures is passed beneath the sinus at two points as indicated. One piece of silk is cut. A proximal and a distal ligature and a mattress suture are thereby provided. These are tied as in c and the sinus is opened. Four cardinal everting mattress sutures are placed between sinus and artery as shown in (d). The anastomosis is completed by a continuous everting suture as in (e). Trauma to sinus is minimal to prevent thrombosis. (J. A. M. A.).

Pott-Smith-Gibson clamp enabled us to open the aorta and to make anastomosis to the aorta. In patients with extensive arterial disease it will be desirable to select a segment of aorta that is free of disease. A free graft of vein or artery was used in our experiments. We used a free graft of brachial artery in one patient upon whom this operation was done. This artery had atheroma

FIG. 3.—Free graft of vein between aorta and coronary sinus of the dog. The aorta is dissected free for a distance of about 3 cm. Two intercostal arteries are cut. The special clamp is placed on aorta as in (a.) allowing some blood to pass the clamp. The aorta is opened by inciscion about 5 mm. in length. An everting mattress suture is placed between garft and aorta at each end of this incision. Anastomosis is completed by a continuous everting suture as in (b.) (c.) shows the complete operation.

in its wall. It appears that a vein is preferable to artery and we are using vein grafts at the present time. Observations of the grafts will be made in experiments that have gone along one or two years.

Recently we found that the size of the graft was a factor in the success of the experiment. We made incision in the aorta about 5 mm. in length.

We used a graft of jugular vein. The incision in the sinus was about 5 mm. in length. After the anastomosis was completed we found that the heart did not always tolerate the anastomosis. Frequently failure developed as the chest was being closed or within 24 hours. At the present time we are constricting the graft of the jugular vein so that it will be about the same size as that of the carotid artery. This is done by placing a ligature of silk around the vein so that the inside diameter is about 3 to 3.5 mm. We found in the dog that the heart tolerated the current delivered from the common carotid artery. No doubt there is an optimum amount of blood for the heart. It is possible to deliver too much blood to the heart.

In so far as I know this is the first time a new branch from the aorta has been made. This anastomosis has several advantages. The aorta and the sinus are in one surgical field. The technic is not difficult. There are problems of thrombosis on which we are working at the present time. We expect to determine patency by exploration after the anastomosis has been made and keep about 25 dogs with patent anastomosis for one to three years for observation in long term experiments.

Preparation of the Sinus for Anastomosis. Anastomosis to the normal sinus in the dog was possible in the occasional experiment. As a rule the normal sinus in the dog was so delicate that sutures could not be placed without tearing the sinus. We found that ligation of the sinus resulted in some thickening and fibrosis of the wall of the sinus. This made it possible to place sutures more satisfactorily. In most of the experiments changes in the sinus were continuous and after several weeks the sinus was small and the wall fibrotic. The optimum time for anastomosis was 8 to 14 days after ligation. Occasionally the sinus was satisfactory for anastomosis six months later and there appeared to be variation in the fibrous thickening.

Measurements of Benefit. In view of the technical problems that had to be overcome in order to develop this operation we were particularly desirous to know whether the anastomosis was beneficial. We spent 18 months working on this project before we had any definite evidence that it would be beneficial. We now have an answer to this aspect of the project. The anastomosis is beneficial and the degree of benefit appears to be significant.

Measurements of benefit were made by complete ligation of the descending ramus of the left coronary artery at its origin and then determination of results. In a normal control group of dogs ligation of this artery was followed by early death, i.e., within 24 hours in 7 out of 10 animals. Only three recovered. In another group of dogs with patent anastomosis between carotid artery and coronary sinus ligation of this artery was followed by no early deaths in 10 animals; there were two delayed deaths, one after 8 days and one after 13 days; the remaining eight animals continued to live.

The amount of destruction in myocardium was equally significant. In the three animals of the control group a large infarct was present in each specimen. The destruction of myocardium involved the entire thickness of myocardium

(Fig. 4.) In the group with patent anastomosis the destruction of myocardium was absent or slight. In this group all 10 dogs lived so that there were 10 specimens for examination whereas in the control group there were only three specimens for examination. Out of the 10 there were four that showed no infarct, and in the remaining six the destruction of myocardium was not extensive in any specimen. (Fig. 5.)

These two measurements of benefit—mortality and infarction—indicate that the anastomosis can and does supply the myocardium with a significant quantity of arterial blood. It would appear that the anastomosis enables one to ligate a major artery with little or no mortality and with little or no infarction.

Effectiveness of this Circulation. The measurements of mortality and infarction after coronary artery ligation indicate that arterial blood in the

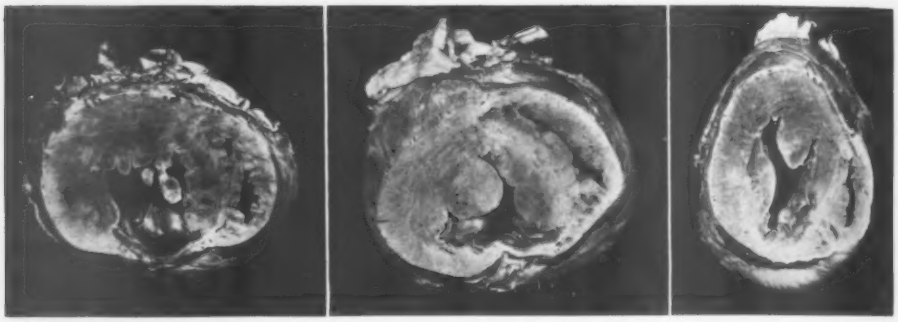


FIG. 4.—Infarcts in the control group. The descending ramus of the left coronary artery was ligated in a group of 10 dogs. Only 3 animals survived this ligation and each of these specimens showed a large infarct. Compare with Figure 5.

venous system is an effective functional circulation. These measurements can be regarded as proof of the effectiveness of this circulation. Additional information on this point was obtained by injection studies of dead specimens. The dog was bled; the blood was heparinized and the heart was removed. The coronary sinus was cannulated as was also the left coronary artery. Blood was injected into the sinus under pressure of 120 mm. mercury. The amount recovered from the artery was measured. In normal hearts the average amount recovered from artery was 9 cc. per minute. In another group of experiments the coronary sinus was ligated and several weeks later similar determinations were made. The average amount recovered from the artery was 22 cc. per minute. On the basis of these experiments it would appear that blood can enter the arterial bed from the venous bed. It would also appear that larger quantities of blood can enter the arterial bed after the sinus has been occluded. This point may have significance in reference to the functional characteristics of retrograde flow. Does this arterial blood in the venous system have the same functional possibilities in reference to oxygen-exchange

as does blood in the arterial system? Does any of the arterial blood from the venous side by-pass the capillary bed and escape into the chambers of the heart without giving up its oxygen? We have no studies on this subject.

It is possible for blood to by-pass the capillary bed by another route. This

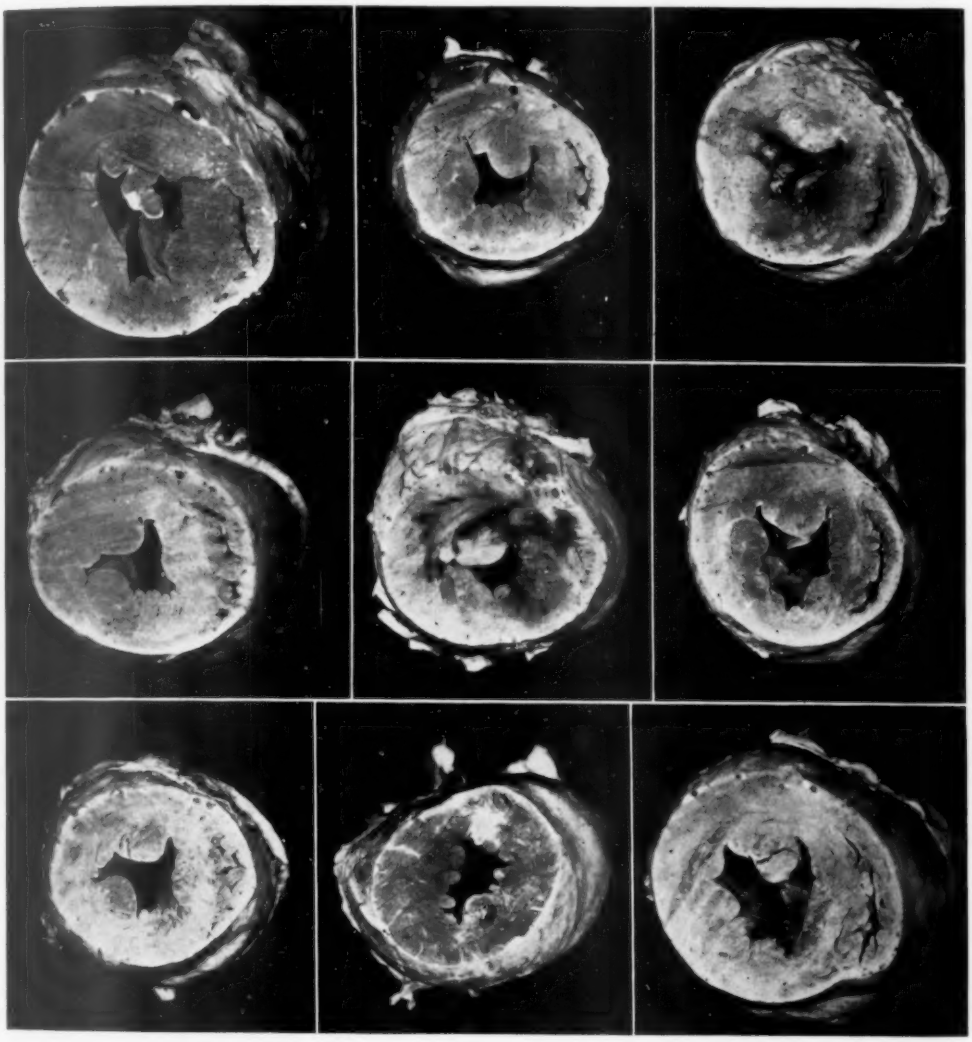


FIG. 5.—Infarcts in group with anastomosis between artery and coronary sinus. The descending ramus of the left coronary artery was ligated in a group of 10 dogs. There were no immediate deaths after this ligation. In 4 specimens there was no infarct. In the other specimens destruction was minimal and appeared in scattered areas. In no specimen was extensive destruction of myocardium found as occurred in each of the control group. Each specimen in Figure 3 and Figure 4 is mounted in the same relative position. The infarct is inferior and between left and right ventricles. The grafted artery can be seen in several specimens. In the middle specimen of the bottom row a scar is seen anteriorly. This occurred because the circumflex ramus of the left coronary artery was accidentally ligated at the time of anastomosis. The small infarct following ligation of the descending ramus of the left coronary artery lies opposite this scar in a papillary muscle.

is by way of the superficial veins that drain directly into the right auricle. There are a number of such channels under the epicardium of right ventricle both anteriorly and posteriorly. The anastomoses between these veins and the coronary sinus system are variable. In some normal hearts they may be absent; in others there are numerous connections. After ligation of sinus these communications usually, but not always, increase. We injected and cleared approximately 30 specimens after arterialization of the sinus and in about half of the specimens these communications were abnormally developed. In two specimens these communications resembled arteriovenous fistulae. These veins could be ligated at operation when anastomosis is done. We expect to get evidence in favor of ligation of these veins. Perhaps a row of superficial sutures around the right auricle may be necessary to prevent further development of these veins. The usual appearance after arterialization is shown in Figure 1B.

Application to Patients. One patient was operated upon. This patient, a man 45 years old, had angina pectoris for five years. He was almost totally incapacitated. Electrocardiogram did not show evidence of an infarct.

Operation was done January 27, 1948. A segment of left brachial artery was used for the graft. The graft had some atheroma in the wall. The aorta was markedly dilated. Anastomosis was made between aorta and graft. The pericardium was adherent to the heart. It was separated from the sinus. Dissection of the sinus was carried out. Stabilizing sutures were placed in the pericardium. The heart beat became weak and blood pressure could not be obtained. Adrenalin was given and heart action improved. The operation was continued. The sinus was dissected from the heart for a distance of one centimeter. An occluding ligature was placed on the sinus toward the ostium. A temporary ligature was placed on the other end of the segment of sinus. The sinus was opened. Anastomosis was carried out between artery and sinus. The heart became weak and blood pressure could not be obtained while the anastomosis was being done. Anastomosis between aorta and graft was completed. The clamp was removed from the graft. The heart beat became stronger after arterial blood entered the sinus.

After the operation was completed the blood pressure rose from 60 mm. mercury to 124 mm. mercury. The patient became conscious. Circulatory failure developed. Death occurred after 24 hours.

Autopsy examination showed recent infarct of posterolateral and basal aspect of left ventricle; arteriosclerosis of aorta; arteriosclerosis of coronary arteries moderate to marked with focal stenosis. Fluid was injected through the graft from aorta into coronary sinus. The anastomosis was patent.

I believe the recent infarct contributed to the cardiac failure. This infarct probably formed during the anastomosis to the sinus when the blood pressure was low.

SUMMARY

1. A third method for revascularization of the heart is presented. This method consists of arterialization of the sinus.

2. Arterialization of the coronary sinus was accomplished by grafting a systemic artery into the sinus and also by making a new branch from the aorta to the sinus using a free graft of artery or vein.

3. Arterialization of coronary sinus is effective physiologically. After anastomosis has been made it is possible to ligate a major coronary artery with little or no mortality and with little or no infarction.

4. Various problems concerning circulation in the heart invite further study.

5. One patient with severe coronary artery disease was operated upon. A free graft of brachial artery was placed between aorta and coronary sinus. A fresh infarct developed in the interventricular septum probably at the time of operation. The anastomosis was patent at the time of death one day later.

I believe we are approaching the time when the operation can be applied to patients. Dr. Gallie in his presidential address, in discussing new operations used the phrase "a large amount of good and a small amount of harm." It is our hope that further experience in application to patients will fall within the broad meaning of his statement.

REFERENCES

[1] Beck, Claude S., Stanton, Eugene, Batiuchok, William, and Leiter, Eugene: Revascularization of the Heart by Grafting a Systemic Artery or a New Branch from the Aorta into the Coronary Sinus. J.A.M.A., **137**: 436, May 29, 1948.

DISCUSSION.—DR. B. NOLAND CARTER, Cincinnati: Dr. Beck's work concerned with surgery of the heart has been not only of great interest to me but has been a most helpful stimulus as well. I did not realize, until I became interested in cardiac surgery, how much fundamental work had come from Dr. Beck's laboratory. No matter what phase of cardiac surgery my group embarks upon, they find that Dr. Beck has already explored the field and made important contributions to it. I have enjoyed his paper today, but not having had experience with the latest operation which he has dealt with, I am not in a position to make pertinent first hand comments concerning it. It is certainly a brilliant technical feat, and one which may well lead to easier and less arduous means of bringing in a new supply to the heart by way of the coronary sinus. The operation is of such recent origin that I feel sure that many questions concerning it which have occurred to Dr. Beck have not had time to be answered. Among those are: (1) How to regulate the flow of a proper amount of blood to the heart; too much might be as harmful as too little. (2) How is venous drainage effected if the venous bed is filled with arterial blood? (3) What will be the result of the production of an A-V fistula so close to the heart? (4) How will patients with severe myocardial damage tolerate this technically difficult procedure?

I have become especially interested in attempting to produce a new blood supply to the myocardium by utilizing the lung as the source. The proximity of the lung to the heart and its extreme vascularity have appealed to me as factors which should make it particularly suitable as a source of blood supply to the heart. The obvious disadvantage of utilizing the lung in this fashion is that the pressure within the pulmonary circulation is so much lower than that in the systemic one. On the other hand, if one is dealing with coronary sclerosis, the pressure in the smaller

terminal vessels in the myocardium is thought to be quite low also and, therefore, could well be fed blood from the pulmonary circuit even though the pressure in the latter is low.

Soon after embarking on the problem of utilizing the lung as a source of blood supply to the heart, I found that Lezius, a German surgeon, had done considerable work along this line in 1939. In brief, our procedure consists in making a large window in the pericardium, painting the surface of the heart and the under surface of the lung with asbestos powder, and suturing the lung to the edge of the pericardial window. In this way, the two surfaces are held in apposition by the sutures in the pericardium and the irritating effect of the asbestos powder, as described by Beck, produces vascular adhesions between the two surfaces. The results of our experiments are shown in the slides.

The operation was performed on 12 normal dogs which were sacrificed at varying intervals. The heart and lungs were removed and a mixture of dogs' blood and india ink was injected at normal pressure into the pulmonary artery of the adherent lobe. Particles of ink were found regularly in the myocardium, but particularly in the superficial vessels.

In the second group the coronary artery was ligated following cardiopneumonopexy; the dog was sacrificed, and injection made. Here the ink was found well distributed throughout the myocardium, as indicated on the slide.

I feel that without doubt we have shown that vascular connections can be made between the vessels in the lung and those in the heart. We have not proven, however, the direction of blood flow nor the volume of blood conducted by the new channels. There was a striking difference between the amount and distribution of the ink in those cases in which ischemia had been created by ligation of the coronary artery versus the normal cases. This bears out the theory that an organ in need of blood will obtain it through any available source.

Feeling that it is not only justifiable but desirable to apply proven laboratory procedures to human cases, I have operated on two patients, utilizing the above procedure. The first patient was operated on about one year ago and has been strikingly improved, so that he no longer considers himself incapacitated. The other patient unfortunately died 36 hours after operation from an overwhelming infection.

I would like to say in closing how much I have enjoyed Dr. Beck's film, and to congratulate him on a splendid piece of work.

DR. ALFRED BLALOCK, Baltimore: I want to discuss the very interesting work that Dr. Beck has reported. I am sure you know that this problem is being studied in many laboratories since Dr. Beck pioneered in this field. For example, in Canada, Dr. Repstein in Montreal has been conducting such experiments, and Dr. Stenstrom in Victoria, B. C., is carrying out similar work.

Dr. Thomas Johns and I have performed a moderate number of operations in which the carotid artery was brought down and anastomosed to the sinus, as Dr. Beck has described. In 52 experiments the carotid artery was used. In 47 of these the anastomosis was open at the completion of the operation: in 28 of the 47, an end-to-end anastomosis was performed, and I believe Dr. Beck described that as the method he used; in the remaining 19 an end-to-side anastomosis between the end of the carotid artery and the side of the coronary sinus was performed. Of the 28 animals in which end-to-end anastomosis was performed, 57 per cent died within 72 hours of operation; the anastomosis was patent in most of them at the time of death, and there was marked engorgement of the superficial third of the muscle of the left ventricle and the adjacent part of the right ventricle. Of the 12 animals out of 28 who survived the end-to-end anastomosis for a longer period than 72 hours, there was thrombosis at the time of autopsy, in 10 of the 12.

It looks as though most of the animals die unless thrombosis occurs. In other words, as Dr. Carter has intimated, it may be that the carotid transports too much blood.

Turning to the end-to-side anastomosis, in which the blood could flow to the right auricle, 16 of the 19 animals survived for an extended period. At the time of autopsy the anastomosis was thrombosed in 10 of the 16. In five of the six, all the blood seemed to be going into the right auricle instead of in retrograde fashion. In the remaining one of the six, the sinus had become occluded just before its entrance into the auricle and backward perfusion was taking place. Thus, in these two groups of end-to-end and end-to-side anastomoses, there were only three in which backward perfusion of the sinus was occurring, and I would like to show slides of the autopsy appearance of these three. The coronary sinus was markedly dilated and thickened in these three cases.

An effort was made in five experiments to conduct arterial blood to the coronary sinus by using a plastic tube, one end of which was placed in the left ventricle and the other in the coronary sinus. In one of these, the tube was observed to be conducting blood 72 hours postoperatively. In the others, allowed to go a longer time, thrombosis occurred.

I think one must conclude that even if this type of shunt or bypass operation is proved to be sound from a physiologic viewpoint, one should hesitate to use it clinically because of the technical difficulties and the associated high mortality.

DR. SAMUEL A. THOMPSON, New York: I should like to take this occasion to state that the work we have done was stimulated originally by Dr. Beck. We have just completed the follow up study of the surgical treatment of coronary disease in a series of patients, some of whom were operated on almost nine years ago.

We prefer to consider this method not so much as a surgical treatment of angina, but as a surgical rehabilitation of the coronary cripple, especially since all these patients were more or less completely incapacitated and were actually cardiac cripples. The criteria we use to determine the degree of rehabilitation are (1) Relief of angina or pain; (2) increase in exercise tolerance; (3) ability to take care of their daily needs so that ordinary moving and travel is possible; (4) return to their former occupation or at least a gainful occupation.

The method consists in the intra-pericardial use of U.S.P. talcum powder, and by this method we produce a collateral circulation to the heart which is both intra- and extracardiac, by the establishment of pericardial adhesions, plus myocardial hyperemia. This myocardial hyperemia is the result of the talcum foreign body reaction, and is a prolonged hyperemia. So far as we can determine it is a form of talcum powder granuloma, and the characteristics of any granduloma are an increase in the number of capillaries and hyperemia. This, of course, is just the reverse of the myocardial ischemia which occurs in coronary disease. These granulomas last for many years.

The degree of rehabilitation does not occur equally in all patients. In this series of 38 patients, in more than 70 per cent the results were good to excellent; in four of the 38 patients the results were less than 33 per cent improvement, which we classify as poor.

The operation is extremely simple. A portion of the fifth left costal cartilage is removed, the pericardium is opened, the pericardial fluid is aspirated and the talc is widely distributed over the epicardium. The wound is closed without drainage.

The need for rehabilitation becomes apparent from a study of the vital statistics. In 1945, the total death rate in the United States was approximately one and one-half million; almost 30 per cent of these were cardiac deaths, which is the No. 1 killer, and almost 10 per cent, or about 130,000 deaths occur from coronary disease and angina. Not all these coronary deaths were previously crippled, for about 15 per cent

died with the first attack, but it is fair to assume that a large percentage were moderately to severely incapacitated before death.

DR. CLAUDE S. BECK, Cleveland: There is much that I should like to say but the hour is getting late. Dr. Carter has raised several questions I should like to try to answer. The first question is whether or not too much blood might be delivered to the heart by the new artery. I think we might take a moment to consider the significance of this question. Indeed, with coronary artery disease in the past the important point always concerned too little blood to the heart. Now we are confronted with the possibility of delivering too much blood to the heart. This is indeed a matter of great significance. Can we get too much blood to the heart? The answer to this question is that it does seem possible to deliver too much blood to the heart. The amount of blood delivered by the graft of jugular vein, as shown in the motion picture, was too much to be tolerated by the heart. In the past months we have learned that the jugular vein graft must be constricted so that its inside diameter is about 3.5 cm. It would appear that there is an optimum blood flow for the heart and, no doubt, in patients this optimum amount will vary with the severity of the disease in the coronary arteries.

The second question concerns venous drainage of blood from the myocardium. When the sinus is ligated blood must escape from the heart by other routes. It seeps through the various channels in the heart and escapes into the four chambers of the heart. In our experimental work on dogs we found that the sinus should be ligated as the first step in the operation. Many sinuses are thin and delicate so that anastomosis in the dog is not possible. After the sinus has been ligated the wall of the sinus becomes somewhat thickened and is more readily manipulated at operation. We found from five to ten days to be the optimum interval between ligation and transplantation.

The third question raised by Dr. Carter concerns arteriovenous fistulae. There are some superficial veins over the right ventricle both anteriorly and posteriorly which can drain blood away from the coronary sinus system and empty the blood into the right auricle. These veins are variable both in dogs and in patients. It is possible for these veins to drain blood away from the myocardial bed producing in effect an arteriovenous fistula. We found such communications in two of our specimens. I have been concerned about this aspect of the problem. I feel that possibly these veins might have to be ligated around the auricle. However, since there is an optimum ceiling that should be placed on inflow into the sinus, these veins may become something of a compensatory mechanism. They cannot keep on enlarging after they reach a certain point because the inflow cannot go beyond the limitation of the graft. This condition is not analogous to congenital arteriovenous fistulae where the development may be progressive. My opinion is that venous communications will not seriously interfere with the circulation. We want to make some long term experiments on this problm.

The fourth question by Dr. Carter concerns myocardial damage in reference to the patient being able to tolerate the operation. I can only say that a patient with coronary artery disease is not a good risk for any operation. Some of our patients have died without operation. Once we get arterial blood into the sinus I think there will be improvement of the heart and that this improvement will, indeed, be significant.

The last part of this discussion concerns thrombosis. We have had about 50 or 60 patent anastomoses. We know when we make a satisfactory anastomosis and when we make an unsatisfactory anastomosis. We know what the factors are for success. The incidence of thrombosis is directly proportional to the amount of operative trauma. I think a solution of this problem is possible.

THE FACTOR OF RATE OF TRANSFUSION WITH PARTICULAR REFERENCE TO THE INTRA-ARTERIAL ROUTE*

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A SURGEON'S ABILITY TO CONDUCT a patient safely through the hazards of an operation depends largely on his understanding of pathologic physiology and his ability to act in the light of this knowledge. The increasing frequency and complexity of operations done on the major blood vessels, including operations for portal bed hypertension, coupled with the trend toward more radical procedures for cancer have made a better understanding of hemorrhagic shock and its treatment a matter of great and pressing importance.

A study has been undertaken in which particular emphasis was placed on the route and rate of administration of the blood and fluids used to combat shock.

Although the bone marrow and corpus cavernosum of the penis have been used in emergencies, the intravenous and intra-arterial routes remain the best avenues through which fluids may be introduced rapidly into the vascular bed. Libraries have been written on the matter of intravenous transfusion and the hazards involved and safeguards required in its use.

Relatively little has been written on arterial transfusion although it now appears to be a most useful weapon in combating shock under certain circumstances. In his first contribution to surgery Halstead[4] mentions the use of this route in the treatment of carbon monoxide poisoning but since his work antedated the time when blood transfusions were safe, it was not applied in shock therapy. Except for sporadic mention of the matter, the literature contains no extensive study of arterial transfusion until 1943 when Drs. Kohlstaedt and Page,[5] acting on the suggestion of Col. Sam Seeley, undertook to investigate the possible usefulness of the intra-arterial route. They subjected a series of 40 dogs to prolonged hemorrhagic shock and then replaced 50 per cent of the shed blood. In one half of the dogs the blood was replaced intravenously, and in the other, intra-arterially. Seventy-five per cent of the intra-arterial group survived as compared with 30 per cent of the intravenous group. Using the same degree or stage of shock (measured by the animals' blood pressure response to standard doses of angiotonin), they found that the re-infusion of all the shed blood would result in nearly 100 per cent recovery no matter which route was used. They concluded that when the arterial route was used less blood was needed and that a more prompt and longer lasting elevation of the blood pressure was obtained. In a second group of experiments[6] these same authors found that:

"(1) The delivery of blood into the aorta perfuses the coronary vessels,

*Read before the American Surgical Association, Quebec, Canada, May 29, 1948.

relieving myocardial ischemia, and since myocardial ischemia probably underlies the cardiac dilatation and insufficiency, places the heart rapidly in a state in which it can pump the infused blood to other areas; (2) when, before the infusion, the patient may have been apneic, at its start he will take a deep breath, as if the arterial filling had rapidly extended to the vital medullary centers; (3) in contrast with intravenous transfusion, blood pressure is rapidly restored, and the volume of blood infused is determined, not by time-consuming analyses or by guess, but by the actual capacity of the vascular tree; and (4) a subsidiary advantage lies in the fact that latent bleeding which causes arterial pressure to fall off rapidly is detectable within minutes rather than hours."

Gardiner[2] has described the successful use of arterial transfusion in connection with a technic of deliberately inducing hypotension as an aid in

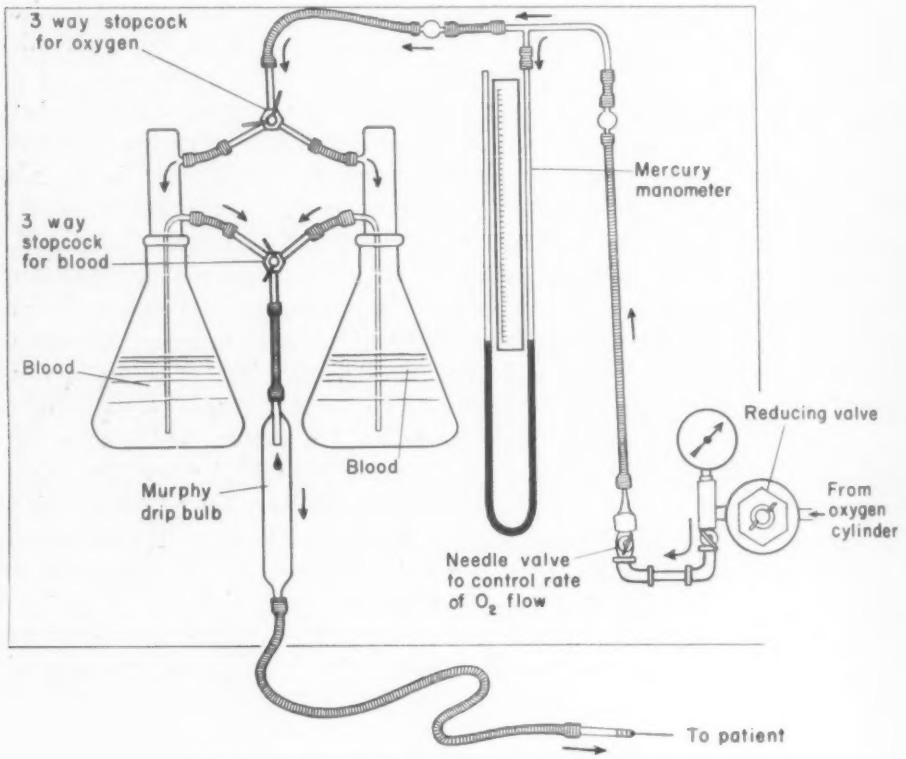

Fig. 1.—Diagram of pressure transfusion apparatus.

hemostasis in the removal of olfactory lobe meningiomas and in the fenestration operation.

At the 77th annual meeting of the Society of Clinical Surgery, Trincher and Elkin[7] reported preliminary experiments on arterial transfusion. They found that in animals in hemorrhagic shock peripheral blood flow (plethysmograph) was returned to normal levels much more rapidly when the arterial

route was used than when the venous route was employed. This report of Trincher and Elkin prompted the studies which are described in this paper.

Although our study is primarily clinical, certain animal experiments have been performed in order to gain experience with the technic and to evaluate, if possible, the effect of using the arterial route on the phenomenon of irreversible shock. Details of the experimental studies will appear in a separate

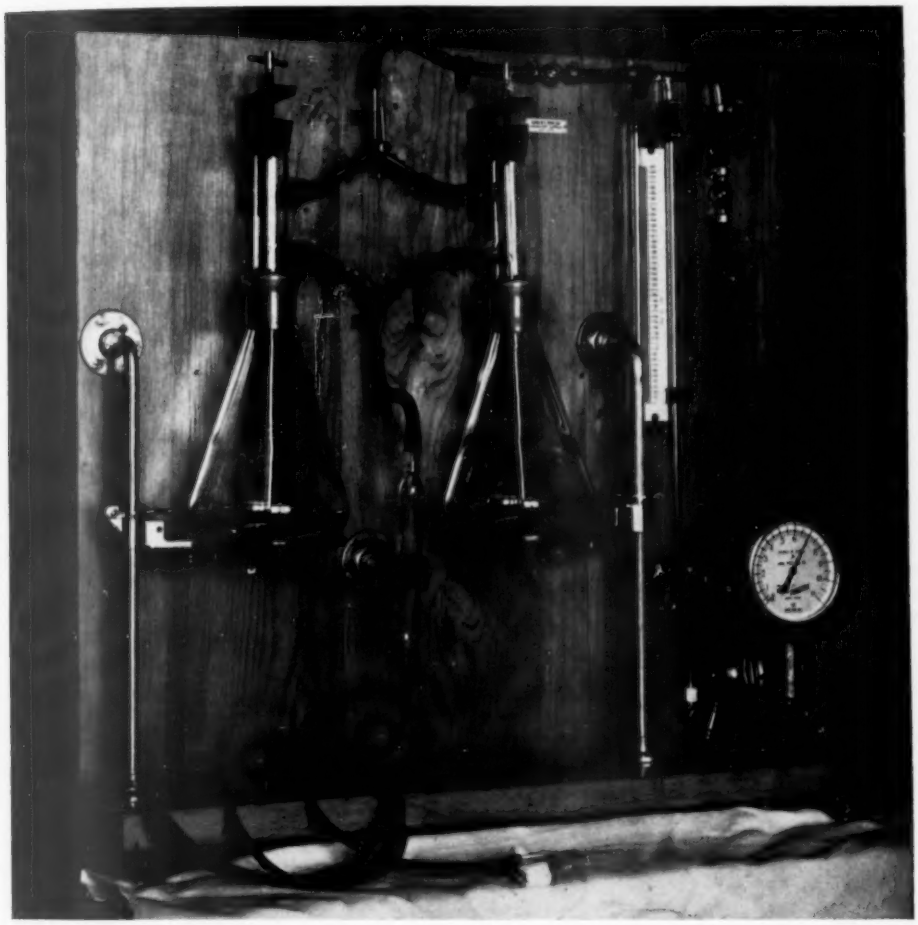

Fig. 2.—Front view of pressure transfusion apparatus.

communication. The lessons learned in these animal studies which have been applied in clinical work are as follows:

(1) Irreversible shock when established according to the criteria set forth by Frank, Seligman and Fine[1] was not favorably influenced by arterial transfusion. Normal blood pressure was restored temporarily, but the animals died of shock within six or eight hours.

(2) The rapid introduction of blood into an artery with the consequent distention of the vessel is a stimulus which often throws the vessel into

spasm. This can be so severe as to interfere markedly with the transfusion. Procaine 1% used locally around the vessel overcomes the spasm. We have supplemented this with stellate ganglion blocks in some of our clinical cases.

(3) Blood pressures more than 20 mm. of mercury higher than the animal's normal could not be obtained although efforts were made to push it higher using very rapid high pressure arterial transfusion. This was apparently due to the animal's own compensatory vasomotor mechanisms.

(4) Congestive heart failure was not encountered in 15 dogs in hemorrhagic shock regardless of the rate of transfusion. This suggests that the cautious gradual increase in the speed of transfusion recommended by Kohlstaedt and Page may not be desirable in advanced shock states where immediate massive replacement of grossly depleted blood volume is needed. We have not encountered congestive failure in our clinical intra-arterial cases.

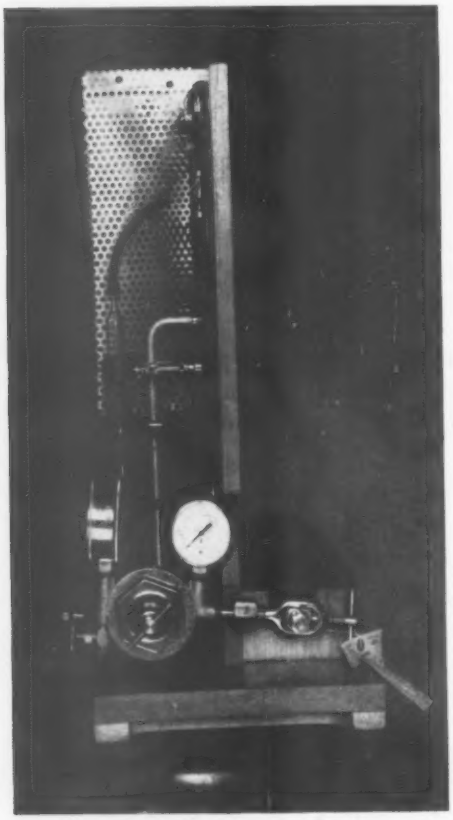

Fig. 3. — End view of transfusion apparatus.

METHOD

An apparatus has been constructed for introducing fluids under pressure into the veins or the arteries. (Figs. 1, 2, 3.) Blood or other fluid is forced from sterile containers by building up oxygen pressure over its surface. The rate of transfusion is regulated by varying the pressure of the oxygen. A fine needle valve and a mercury manometer permit accurate control. At an oxygen pressure just exceeding the patient's diastolic pressure about one drop of blood will enter the artery during each diastole. Rates up to 500 cc. in three minutes, and faster, can be achieved at oxygen pressures in the range of 250-300 mm. of mercury.

The use of two blood containers connected by three-way valves permits the addition of more blood to the system without interruption of the transfusion. Parts of the machine through which blood passes are easily removed for cleaning and sterilization.

In operating the apparatus care has been taken not to let the blood bottle in use become empty thus allowing air embolism to occur.

The venous pressure machine employed is of the standard type. (Fig. 4.)

Intravenous Technic. Although massive intravenous tranfusion can be successfully accomplished through multiple needles with gravity flow, it is possible with the pressure apparatus to obtain rapid flow through a single needle. This makes for greater convenience and readily permits adjustment of the rate of flow through a wide range.

A 16-gauge three-part Lindeman needle is placed in a peripheral vein and connected by means of a three-way stopcock with the pressure transfusion machine and the venous pressure apparatus. The latter is used to take frequent

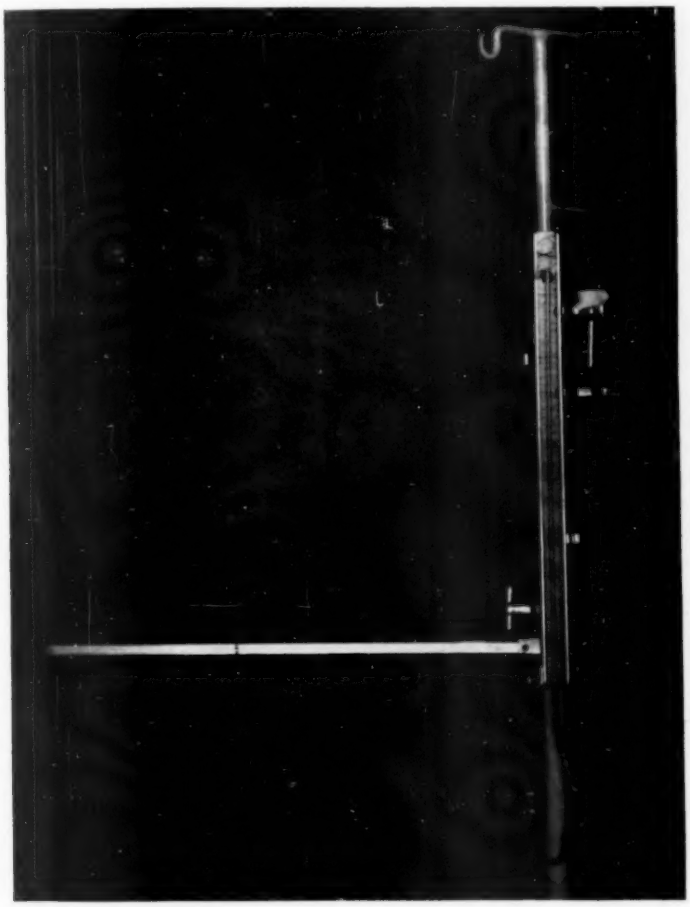

Fig. 4.—Venous pressure apparatus.

venous pressure readings during the period of transfusion. It has not been necessary to tie the needle into the vein.

Intra-arterial Technic. Any artery can be used in giving an arterial transfusion. If a major vessel such as the aorta or iliac artery is exposed in the wound, it may be selected; however, it has usually been more convenient to use the radial artery at the wrist. This is exposed through a short trans-

verse incision and delivered from the wound. A 16-gauge Lindeman needle is then introduced centrally under direct vision and does not need to be tied in. This needle is connected directly to the pressure transfusion machine. One per cent procaine is injected locally around the artery to overcome spasm. This is sometimes supplemented by a stellate ganglion block but this is not usually required. Pressures sufficient to cause a slow drip and keep the needle patent are used until rapid transfusion becomes necessary.

Except in dire emergency, blood is the only fluid which we have introduced into the radial artery.

At the completion of the transfusion the needle is withdrawn. If bleeding continues from the puncture site, the vessel is ligated; but this is often unnecessary, if pressure is maintained at the opening for a few minutes.

Venous pressure should be followed in arterial as well as in venous transfusions.

CASE REPORTS

Case 1. A 57-year-old white woman was admitted with diabetes mellitus, a moderate degree of myocardial damage, and longstanding abdominal echinococcosis. While on the medical ward she had two massive gastro-intestinal hemorrhages. Five transfusions of 500 cc. of blood brought her count up to 4.4 million by the day of operation. At operation great difficulty was encountered in removing an enormous spleen which was adherent to all nearby structures. Splenectomy permitted visualization of the stomach where a large echinococcus cyst was found to have eroded through the lesser curvature of the stomach from the liver, causing the bleeding. A large amount of blood was lost during operation. Shock developed in spite of 500 cc. of blood and 500 cc. of gelatin given intravenously. Arterial transfusion was begun and the pressure returned from 0/0 to 110/70 within fifteen minutes. In that time 500 cc. of blood was given intra-arterially. During the remaining two hours of the operation another 1000 cc. of blood and 500 cc. of gelatin were given intra-arterially. It was found that the systolic blood pressure could be kept at any level between 60 and 100 by varying the rate of flow of the transfusion. The patient left the operating room with a pressure of 100/60 but died 24 hours later. Although systolic pressures of 100 were obtained intermittently during this period, the shock state was never really overcome, perhaps because of severe myocardial disease. No autopsy was obtained.

Comment. This was our first clinical case, and in spite of the unfavorable outcome, offered encouragement to proceed with additional trials of arterial transfusion. There is no reason to suppose that the gelatin solution employed in this case played an unfavorable part in the outcome but, for reasons stated below, we prefer not to administer solutions other than blood through the arterial route. In retrospect it would appear that much larger quantities of blood should have been given during the operation as well as during the post-operative period.

Case 2. A 15-year-old white girl was admitted with typical signs and symptoms of coarctation of the aorta. Anteoperative blood pressure in the arms was 180/110 but none was obtainable in the legs. Operation: Resection of coarctation with end-to-end anastomosis of the aorta. (See Figure 5 for details of the blood pressure during operation.)

The transfusion was given centrally up the right radial artery. During the early part of the operation the pressure was regulated so that only a few drops entered the patient on each diastole of the heart (A). When the aortic clamps were removed (B) and the

pressure plunged to 0/0, the transfusion was speeded up and 300 cc. of blood was run into the artery in three minutes. As shown in Fig. 5, the pressure rose almost immediately and was thereafter well maintained by the patient. The slow drip of saline intravenously was given so that a patent needle in a vein would be immediately available if the arterial route was not successful.

This patient has had a good result from her operation and no detectable effect from the ligation of her radial artery.

Comment. We have since done three other cases of coarctation. In none of them did the need for transfusion develop, and the arterial route was used simply for replacement of the amount of blood lost. In one case in which

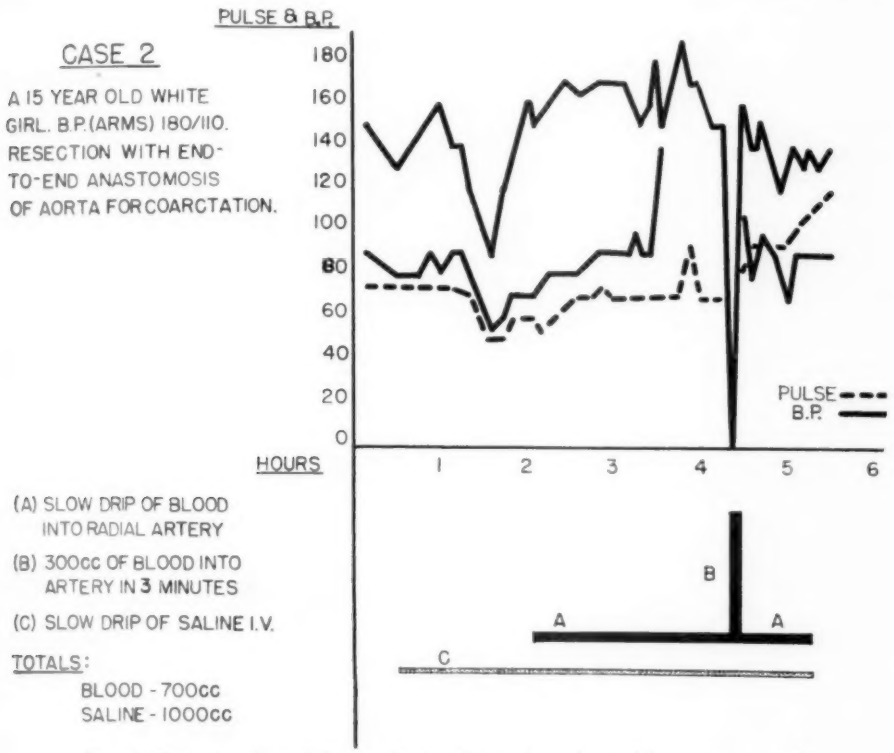

FIG. 5. Case 2.—Arterial transfusion in conjunction with resection and anastomosis for coarctation of the aorta.

massive (600 cc.) hemorrhage occurred from the aortic arch, immediate arterial transfusion prevented any perceptible change in the blood pressure. When the sterile drapes were removed at the end of the procedure in that case, the skin over the radial artery into which the arterial transfusion had been given showed a cyanotic streak 3 to 4 cm. wide and extending from the wrist to the elbow. This disappeared promptly when the arm was adducted and the forearm elevated.

Case 3. A 59-year-old woman suddenly developed shock while awaiting elective wiring of a large aneurysm involving the left common iliac artery and the distal portion of the aorta. Emergency celiotomy disclosed considerable abdominal hemorrhage from the

aneurysm, and wiring of the aorta proximal to the aneurysm was performed. Blood was given by arterial transfusion, and gelatin was administered intravenously. Following one particularly massive blood loss, a period of three minutes was required to bring the blood pressure from zero to 105/70 by acceleration of the rate of arterial transfusion. Otherwise the blood pressure was maintained within a safe range in spite of the initial condition of hemorrhagic shock and considerable continuing blood loss. The condition of the patient was good at closure.

Comment. It is likely that the same result could have been achieved by use of venous transfusion under pressure.

Case 4. A 37-year-old man underwent celiotomy for peritoneal abscess and multiple spontaneous ileo-ileostomies developing secondary to a skip type of regional ileitis. The

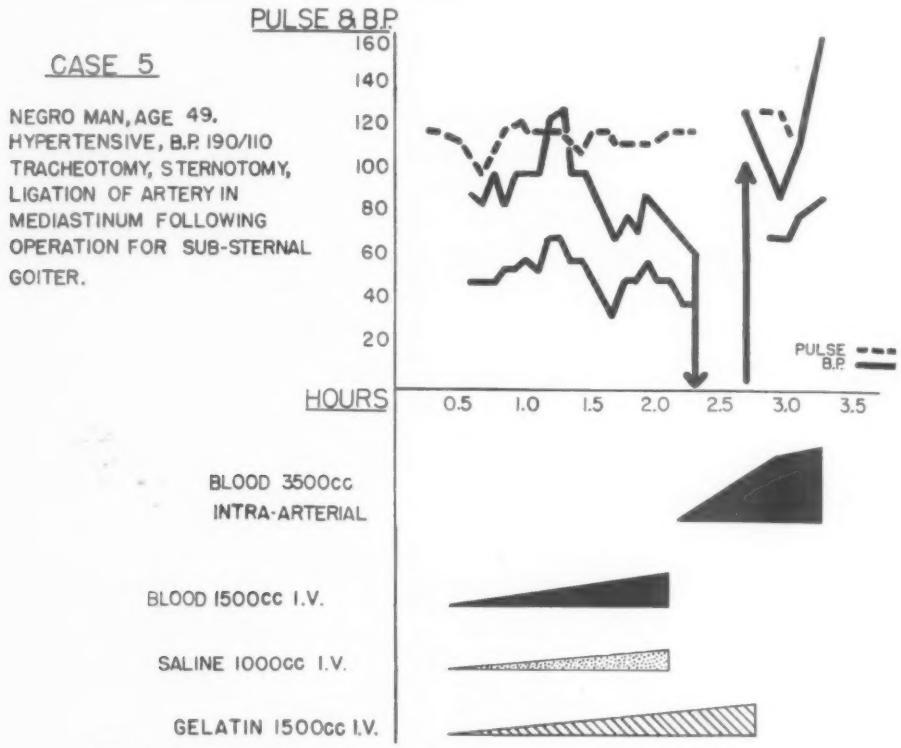

FIG. 6. Case 5.—Arterial transfusion for resuscitation following severe post-thyroidectomy hemorrhage.

ileum involved in the ileo-ileostomies was resected and primary anastomosis was performed, leaving approximately three feet of small bowel. Arterial transfusion was begun while the operation was in progress because of severe shock not controlled by venous transfusion. In spite of a long operation and heavy, continuing blood loss, blood pressure was maintained by varying the rate of arterial transfusion. The patient left the operating room in good condition. Total amount of blood administered was 6500 cc., of which 4000 cc. was given intra-arterially, and hematocrit the following day was 42 per cent Purplish discoloration and vesiculation of the skin over the radial aspect of the forearm receiving the arterial transfusion developed after operation, but did not progress beyond the stage of superficial necrosis.

Comment. In view of the extensive unavoidable blood loss which occurred

during the operation, only rapid transfusion could have afforded the necessary support to the patient.

Case 5. A 49-year-old hypertensive negro man whose blood pressure normally is 190/110 underwent partial thyroidectomy for a large, substernal, non-toxic, nodular goiter. The operation went well and the gland was removed without splitting the sternum. The patient was returned to the ward in good condition. About an hour later his airway was found to be obstructed and an emergency tracheotomy was done in bed. He was then taken to the operating room where the neck was exposed. Brisk bleeding which could not be controlled by extensive packing with oxidized gauze was seen to be coming from the area beneath the sternum. (See Fig. 6 for details of course in operating room.) When the neck exploration was started, his pressure was 90/50, which was serious hypo-

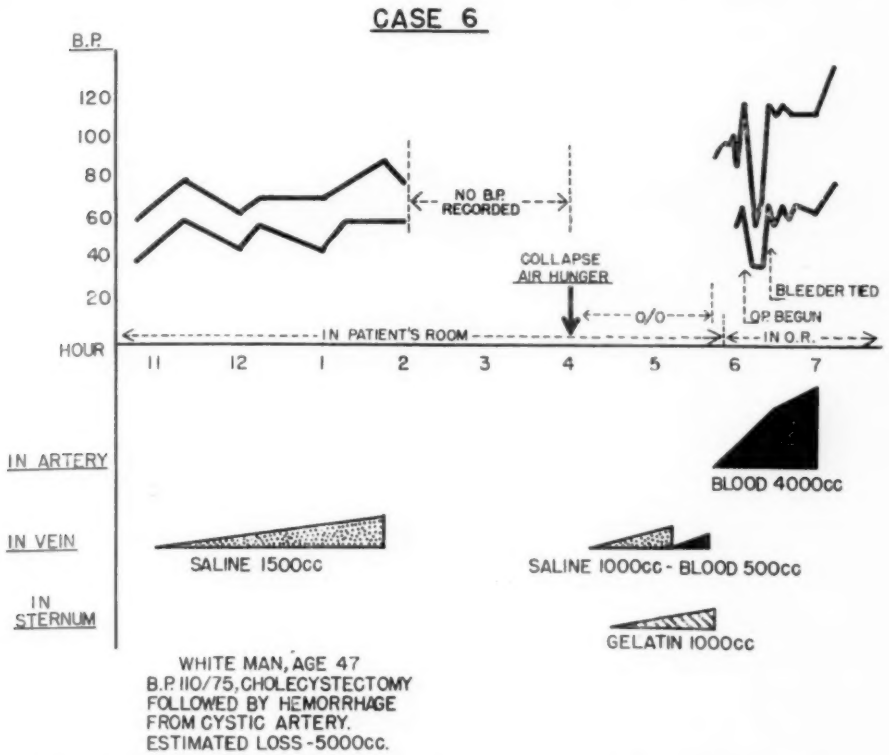

FIG. 7. Case 6.—Arterial transfusion for resuscitation following deep shock resulting from cystic artery hemorrhage.

tension in view of his excessively high normal pressure. During the next one and one half hours 1500 cc. of blood, 1000 cc. of saline and 1500 cc. of gelatin were given intravenously. In spite of this the blood pressure gradually fell to 60/40 and the pulse stayed in the range of 110 and was of poor quality. At this point it was decided that the sternum would have to be split in order to secure the bleeding point. With the first blow of the mallet on the sternum knife the pressure fell to 0/0. Intra-arterial transfusion was then started at once. About 30 minutes later after 2000 cc. had been given, the pressure was again measured to be 120/70. The bleeding vessel was found to be the left thyrocervical trunk, which was ligated. Total parenteral therapy of 5000 cc. of blood and 1500 cc. of gelatin. The patient did well postoperatively although his red blood count

showed an anemia of 3.2 million for three days postoperatively. This was corrected by further transfusion.

Case 6. A white man, age 47, underwent an uneventful cholecystectomy for chronic cholecystitis and cholelithiasis. His normal blood pressure was 110/75. He was returned to his room with a pressure of 60/40 which was thought to be due to a postanesthesia reaction. 1500 cc. of saline was given intravenously and he was watched carefully. At the end of four hours he seemed in good condition, although blood pressure was only 80/50. During the next two hours his blood pressure was not taken. Five and one-half hours postoperatively he suddenly collapsed and was found to have air hunger, unobtainable blood pressure, feeble pulse and a cold sweat. A vein was immediately exposed and 1000 cc. of saline and 500 cc. of blood were pumped in under pressure with a large syringe—at the same time 1000 cc. of gelatin was forced into the sternal bone marrow. In spite of this his pressure remained unobtainable. (See Fig. 7 for details.) An arterial transfusion was begun in the patient's room and it was noticed that more than the usual amount of difficulty was experienced in bringing the blood pressure back to normal. It was not until 1000 cc. of blood had been run in very rapidly (in about eight to ten minutes) that

Fig. 8. Case 7.—Showing necnosis in hand.

measurable pressure could be detected, at a level of 90/70. This slow response confirmed our impression that active bleeding was going on since in the absence of such bleeding much less blood should have caused a more prompt rise in pressure. The patient was taken to the operating room with the arterial transfusion running. Anesthesia was induced and the wound opened. When the wound was opened, a marked fall in pressure occurred. Four thousand cubic centimeters of blood were sucked from the peritoneal cavity and many large clots were removed. Estimated blood loss was 5000 cc. The bleeding point could not be located until the intra-arterial transfusion was speeded and the pressure once again forced up into the neighborhood of 110/70. When this was done, the stump of the cystic artery was found to be the bleeding vessel and it was ligated. A total of 4000 cc. of blood was given intra-arterially in about 75 minutes. The patient did well and was discharged from the hospital in good condition.

Comment. In this case the intra-arterial transfusion aided in making the diagnosis of continued bleeding. Rapid restitution of blood pressure made possible the discovery of the hidden bleeding artery.

Case 7. A 47-year-old woman was subjected to splenorenal vein anastomosis for portal hypertension due to hepatic cirrhosis. Blood loss was approximately 4500 cc.;

5500 cc. of blood was administered by arterial transfusion and 1500 cc. of gelatin by venous infusion during the entire nine and one-half hour procedure. Blood pressure was easily maintained at normal levels, being quickly restored after any sudden drop by acceleration of the arterial transfusion rate. During the nine and one-half hour operation she lay on her right side with the right arm in about 120 degree abduction. The right radial artery received the transfusion centripetally. At the conclusion of the operation when the sterile drapes were removed, the right hand and forearm were cyanotic and cold. These changes were attributed to the unfavorable position of the arm, and it was believed they would prove transitory. The arterial needle was withdrawn and the radial artery ligated. By the fourth postoperative day gangrene involving chiefly the radial portion of the hand was apparent in spite of repeated stellate ganglion blocks (Fig. 8). Death occurred on the sixth postoperative day due to massive esophageal hemorrhage, the splenorenal vein anastomosis being obstructed by thrombus. Postmortem dissection of the arm was not permitted, but arteriograms demonstrated no radial artery shadow in the distal half of the forearm and no radio-ulnar arcade in the hand.

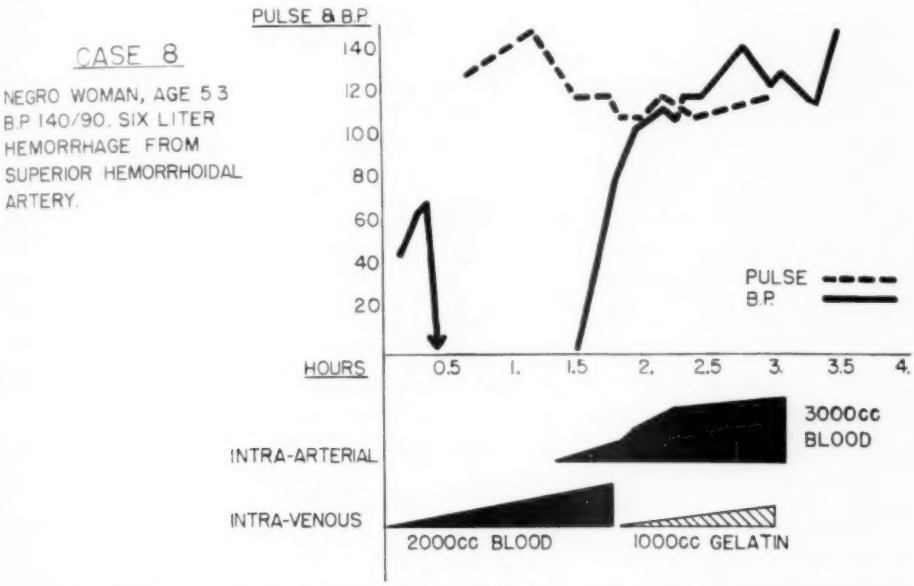

FIG. 9. Case 8.—Rapid intravenous transfusion through multiple needles in conjunction with surgery for massive gastro-intestinal hemorrhage.

Comment. Unfortunately, thrombosis, postmortem blood clot, or congenital anomaly could be responsible for the changes in the arterigram. This complication is difficult to explain because two possible contributing factors exist: (1) Impaired venous return from that arm due to poor position may have resulted in axillary vein thrombosis. (2) The radial artery was ligated at the wrist and the normal radio-ulnar anastomosis of the hand may not have been present. This is the only instance of this type which we have encountered.

Case 8. Eighteen days after abdominoperineal rectal resection for carcinoma a 53-year-old woman suddenly showed signs of massive intra-abdominal hemorrhage. For about 30 minutes neither blood pressure nor peripheral pulse could be detected, in spite of about 1500 cc. of blood transfused by venous route over a period of one and three-quarters hours. After 2000 cc. of blood had been administered by the centripetal arterial route

in 20 minutes, the systolic blood pressure had reached 100 mm. of mercury (Fig. 9). The superior hemorrhoidal artery could then be recognized as the source of the bleeding, and it was ligated. The patient left the operating room in good circulatory condition. Total blood loss was 6000 cc. and hematocrit 18 hours later was 41.2 per cent. Postoperatively the skin of the forearm over the radial artery used for the transfusion developed purplish discoloration and marked vesiculation. Although the hemorrhagic shock was controlled adequately, death occurred on the eighth day from peritonitis and lower nephron nephrosis.

Comment. The need to administer Group 0 blood which had not been cross-matched may have played a part in causing the renal lesion, but other signs of transfusion reaction were not found. The changes of the forearm did not show signs of progressing beyond superficial necrosis during the period of survival.

Case 9. A 66-year-old white man was admitted to the hospital with massive gastrointestinal hemorrhage from a benign gastric ulcer. 3500 cc. of blood was given anteoperatively following which it was decided that emergency gastrectomy must be done because of great difficulty in maintaining adequate blood pressures.

During operation it was necessary to give another 3000 cc. of blood to replace blood lost by hemorrhage and prevent shock. This was done through three large intravenous needles. Venous pressures were taken frequently during the procedure. On one occasion the venous pressure rose to 155 mm. of water and because of this the transfusions were all retarded to slow drips. The venous pressure fell to 50 and transfusions were speeded again to compensate for bleeding in operative field. This type of management was carried out through the operation. The patient did well and his red blood count the next day was 3.2 million.

Comment. By carefully following venous pressure readings we were able to transfuse 6500 cc. of blood into a 66-year-old man in a relatively short period of time without causing congestive heart failure. Possible citrate intoxication was combatted by calcium gluconate administration.

DISCUSSION

1. The choice of route of transfusion is unlikely to influence the course of *irreversible* shock, even provided adequate quantities are given. The recovery of animals from otherwise irreversible shock has been accomplished by Frank et al[1] by cross-perfusion of the liver with oxygenated blood from a donor animal. Their studies indicated that administration of blood and fluids by the portal system may be more effective in treatment of shock than when the peripheral veins are used. We have not yet investigated this aspect of the problem. However, in shock which has not reached a stage of irreversibility, the arterial route appears to make the effects of transfusion available more rapidly to the organism. An added benefit is the direct hydraulic effect of raising the pressure in the aortic arch which will immediately be reflected by increased blood flow in the cerebral, coronary, hepatic, and renal vessels.

2. The rate of replacement of massive blood loss deserves increased emphasis. The amount of blood required for replacement after hemorrhage is underestimated many times (Case 5) as indicated by anemia in the immediate post-treatment period. A frequent error is too rapid introduction of blood by the venous route. This hazard is best avoided by frequent determinations

of venus pressure during the transfusion period. This is especially important to the patient with diminished cardiac reserve. The latter is the often encountered situation when the surgeon finds himself trying to balance the patient on the narrow line between congestive heart failure on the one hand and shock on the other.

3. The fluid changes incident to the treatment of shock impose a heavy strain on the cardiovascular system. If cardiac reserve is not adequate, heart failure may supervene. When time permits preoperative cardiovascular evaluation, such diminished reserve may be discovered and prophylactic digitalization instituted. The importance of this aspect of the problem is supported by recent work of Glasser and Page[8] who transfused dogs after hemorrhagic shock. Of a group given a good prognosis those receiving ouabain showed 71 per cent survival, those not receiving it only 5 per cent survival.

4. With respect to the nutrition of the tissues of the hand and forearm incident to arterial transfusion, two factors are important:

a) Ligation of the radial artery may result in necrosis of a part of the hand in those rare cases where the palmar anastomoses between radial and ulnar arteries are incomplete. Such anomalies are uncommon, however, and this small risk is to be accepted as part of a life-saving arterial transfusion. If time permits, these cases may be discovered by externally compressing the radial artery before operation and observing the effect on the hand. In some adults ligation of the radial artery probably will be necessary.

b) For the arterial route only blood should be used, since it is believed the dilution of brachial arterial blood by plasma, gelatin, or saline increases the risk of ischemic necrosis of the tissues of the forearm and hand. Kohlstaedt and Page administered plasma to three patients via the radial artery. In two of these patients an area of sloughing appeared on the flexor surface of the forearm which had been used for the transfusion.

In our experience four patients receiving blood centripetally in the radial artery showed marked purplish discoloration and coolness of the skin overlying the radial artery in the forearm and in two of these blistering of the skin occurred; in the other two the changes disappeared rapidly. It is believed these changes are due to varying degrees of vasospasm of the primary branches of the radial artery due to the introduction of large volumes of cold blood under high pressure into that vessel. Damage to vasa vasorum and small branches from the high pressures employed may have been a factor.

5. It is important to emphasize that when shock is anticipated more than enough blood should be held in readiness before operation. On occasion as much as 5000 cc. of blood have been cross-matched for a single patient.

6. In resection of the coarcted segment of aorta with primary anastomosis marked hypotension sometimes develops when the aortic clamps are removed after completion of the anastomosis. Peripheral resistance is decreased because the heart has not only a well developed collateral bed but also a normal aortic channel into which to empty. Blood pressure falls sharply until

vasomotor mechanisms make the adjustment, or death supervenes. Artificial hydraulic support of aortic arch pressure appears to be the physiologic antidote to this hypotension. Such a solution is provided by centripetal arterial transfusion.

It is true in most instances that this measure of protection may not be necessary. Nevertheless, one patient operated upon in this hospital died suddenly immediately after removal of the aortic occluding clamps. This occurred before the development of the pressure transfusion apparatus.

SUMMARY

A review of pertinent literature indicates certain advantages of the arterial over the venous route of blood transfusion in the treatment of shock. However, it is possible that some of the benefits attributed to arterial transfusion are actually due to the rapid rate at which the blood had been administered.

An apparatus is described which makes possible prolonged, controlled, rapid administration of fluids through vein or artery. Frequent determination of the venous pressure is essential to avoid development of pulmonary edema during rapid transfusion. In eight cases of severe shock the blood was administered arterially by use of the apparatus described. Recovery occurred in each instance. The relative importance of the route of transfusion on the one hand and the rate of administration on the other is difficult to evaluate. It is possible that an advanced stage of shock may develop on occasion which is irreversible to venous transfusion but reversible if the arterial route is employed. The studies here reported do not answer this question.

During operative procedures characterized by excessive blood loss, and therefore requiring large replacement volume, the ability to control blood pressure through a hydraulic system attached to the arterial circulation is an additional safeguard against shock and a great comfort to the surgeon.

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DISCUSSION.—DR. DANIEL C. ELKIN, Emory University, Ga.: The clinical results of intra-arterial transfusion have closely paralleled the observations which we have

made on laboratory animals. Blood flow to an extremity was selected as a criterion for determining changes to the peripheral blood flow, on the premise that since this flow is restored late in the correction of hemorrhagic shock, flow to vital centers probably had already been restored. In the anesthetized dog, blood flow to a hind limb was measured by use of an air plethsymograph, and recorded optically. The opposite femoral artery was cannulated for controlled hemorrhage, optically recorded blood pressure measurements, and the re-infusion of blood. After a basal period of 30 minutes, normal blood pressures and flows were recorded. The animals were then bled rapidly until the mean arterial pressure reached 50 mm. of mercury. Hemorrhagic hypotension was maintained at this level by repeated small hemorrhages for intervals varying from 30-75 minutes. At the end of this interval, all the blood removed was re-infused, in one group of animals by the intra-arterial route, in the other by the intravenous route. In the intra-arterial group, the blood was re-infused at a pressure approximately 50 mm. of mercury greater than the mean blood pressure and at a rate of approximately 100 cc. per minute. Pressure and flow determinations were made throughout the infusion period and at varying intervals thereafter up to one hour.

The intravenous transfusions were allowed to flow by gravity at a rate substantially greater than that used in the routine clinical administration of blood, and which was considered to approach the maximum pressure permissible to avoid right heart congestion. The rate averaged 25 cc. per minute. When an intra-arterial transfusion was initiated at a pressure approximately 50 mm. of mercury greater than the animal's mean arterial pressure, there was almost instantaneous rise in pressure throughout the arterial system, as noted by recording the pressure in arteries at some distance from the site of transfusion. These flows reached the normal values at an average of about seven minutes, some as quickly as four minutes. Upon discontinuing the intra-arterial transfusion, the arterial pressure and blood flows were maintained indefinitely and recovery ensued in all instances. Following intravenous transfusion, recovery was considerably slower, requiring a period of approximately four times longer. There was also a tendency for blood pressure and flow to be maintained at a lower level than normal after the transfusion was completed.

From our clinical experience, it appears that intra-arterial transfusion has a definite place in the treatment of severe traumatic shock, exsanguination in obstetric emergencies, and intra-abdominal and intrathoracic hemorrhage.

DR. GEORGE H. HUMPHREYS, New York: I would like to acknowledge our indebtedness to Dr. Elkin and Dr. Pilcher for their work, without knowledge of which we would not have undertaken to treat these patients. I can say from experience, especially with coarctation cases, that it is a matter of great reassurance to a physician that he can replace blood rapidly, and I can say that in many cases a fall in pressure could be fatal. It is necessary to have a well-organized blood bank to produce blood rapidly. It should be used only in cases of great emergency.

DR. HILGER P. JENKINS, Chicago: Following the dictum that we should strive to carry out the procedure which will do the most good and the least harm, I would like to suggest that a cuff or a patch of gelatin sponge (gelfoam) be used to control hemorrhage from the arterial puncture wound and thus obviate the necessity and hazards of ligation of the vessel.

This suggestion is based on recent experimental work on dogs, in which it was possible in most instances to obtain control of hemorrhage and restoration of blood flow after a scalpel wound of the coronary artery by the gelatin sponge patch technic.

DR. CLARENCE CRAFOORD, Stockholm, Sweden: There has been some talk about the rapid fall of blood pressure caused by rapid release of the aortic clamps. This is

difficult for me to understand. I have had the aorta cross-clamped in 70 cases of coarctation and patent ductus, and have never taken any precaution to release them slowly, and have no blood pressure fall of significance in connection with removal of the clamps. In cases of patent ductus where there is no collateral circulation, when aortic clamps are applied the blood pressure rises sometimes to 200 mm. of mercury or more, and has dropped to the previous level after the clamps have been released. I do not think the explanation given by Gross is the correct one, that is, that it is the releasing of the clamps that causes the fall in blood pressure. I am convinced that there is some other factor such as unsatisfactory ventilation during the anesthesia for, so far as I know, all these patients are allowed to breathe themselves, and have not been under controlled respiration during the operation. I believe that if adequate ventilation were used, the small additional stress to which the heart is subjected on removal of the aortic clamps would not have affected the heart.

There is a point I would like to stress in connection with giving large amounts of blood rapidly. I believe it better to give fresh blood from heparinized donors, rather than to give old blood. Fresh blood will function much longer than stored blood from a blood bank.

DR. E. I. EVANS, Richmond, Va.: I wish to compliment Dr. Porter highly for this splendid presentation, and not the least for the dramatic effect. After wars are ended we are apt to think we have learned all there is to know about traumatic and surgical shock. In going over recently the work of Cleghorn and Shute from Canada, it is evident to me that a tremendous amount is still to be learned.

For those who still worry about the introduction of whole blood as "foreign material" into the blood stream, we may be reminded of what John Hunter said to his students, "Blood is that out of which all living cells are made and from which they are supported."

DR. RALPH F. BOWERS, Memphis, Tenn.: I am very much interested in the new agents and technics employed in replacement therapy. Intra-arterial transfusion has a place which will prove of inestimable value in some cases. My associations have been with surgeons who stressed careful hemostasis and gentle handling of tissues and, therefore, utilized replacement therapy as an adjunct, when it was not possible to prevent the loss of blood. There is developing a philosophy in surgeons today, the older ones as well as the younger ones, which reflects the sense of false security so far as blood loss is concerned, because we can have a bottle of blood hanging on a pole by the patient's side, which allows us to "lose all the blood we wish" and still save the patient. The blood in the bottle is not as good as the patient's own blood. The recent emphasis placed upon replacement therapy has brought about great improvement of technics and agents. Therefore, great emphasis has been exercised about replacement in the past decade. Instead of applying the emphasis on replacement, we should return to emphasizing the time-honored fundamental principle of hemostasis and vigorously apply thought and energy to the prevention of the loss of the patient's blood during the operation.